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ORIGINAL ARTICLES

IMPORTANCE OF EARLY SURGICAL TREATMENT OF CRANIOSYNOSTOSIS

Review of 36 Cases Treated During the First Six Months of Life

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OPERATIVE procedures for premature closure of the cranial sutures have been performed since before the turn of the century. There have been two principal reasons for many unsatisfactory results: (1) failure to differentiate patients with primary microcephaly, for whom surgical treatment is of no benefit, and (2) failure to recognize and treat craniosynostosis sufficiently early in life to prevent irreversible brain damage, visual loss and extreme degrees of cranial deformity. Although widespread agreement exists among neurosurgeons today that surgery should be undertaken in early infancy,[1-4] there is too often delayed establishment of the correct diagnosis and there are very few reports, therefore, of the results of treatment during this period of rapid growth. The purpose of this paper is to stress the importance of early treatment and to report the authors' experience with patients operated on during the first six months of life.

MATERIAL

One hundred and twenty patients have been operated on in this clinic for craniosynostosis. Thirty-six of these, approximately one-third, have been treated within the 1st 6 mo. of life. These include the following:

1. Nineteen patients with premature fusion of the sagittal suture alone.
2. Ten patients with premature closure of the coronal suture, 5 unilateral and 5 bilateral; the squamosal suture also has been fused in 4 of these patients.
3. Five patients with fusion of 2 or more sutures, 3 of the coronal and sagittal sutures and 2 of the coronal and lambdoid.
4. Two patients fall into a separate category, one with bilateral coronal fusion but persistence of the metopic and the other with premature fusion of the metopic suture alone.

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Premature Closure of Sagittal Suture

Increased intracranial pressure of clinical significance does not ordinarily occur in patients with premature sagittal suture fusion alone until functional closure of the other sutures occurs at about two years of age. Until that time there is compensatory separation

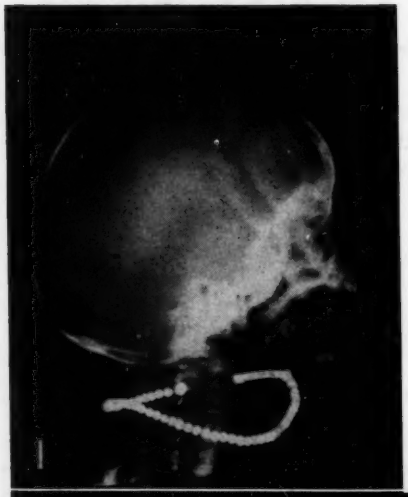
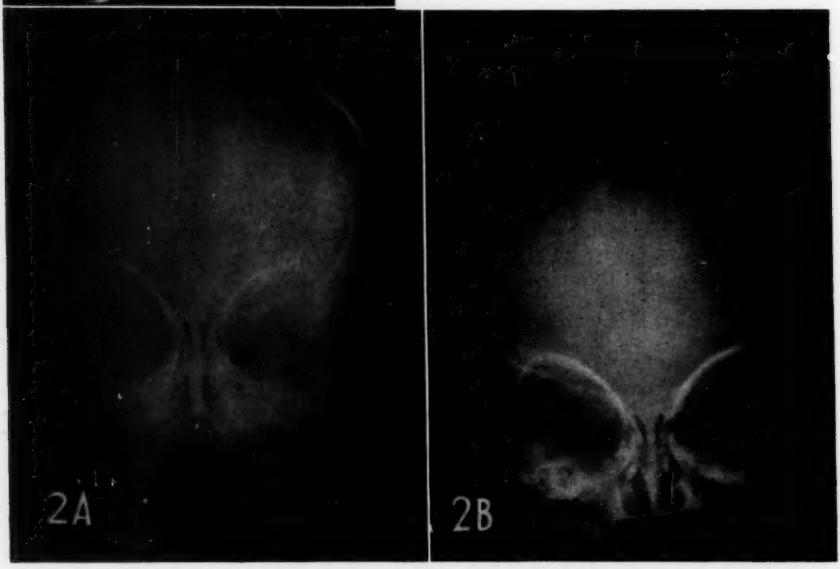


Fig. 1. Premature closure of sagittal suture in 10 day old infant showing compensatory separation of coronal and lambdoid sutures.

Fig. 2. Premature closure of sagittal suture. A. RG immediately following parasagittal craniectomies at age 3 mo. Note absence of sagittal suture and width of operative defects. B. Five weeks later. Note marked spread of defects and increased width of calvarium.



of the coronal and lambdoidal sutures in response to brain growth, thus giving rise to abnormal elongation of the skull (Fig. 1). There is no doubt, however, that some elevation of pressure often occurs during the first few months, as demonstrated by splitting of the coronal and lambdoid sutures and by spread of the surgically-created parasagittal

sutures, which can be seen immediately at the operating table and by roentgenogram during the first few weeks and months postoperatively (Fig. 2).

A convenient method of quantitating the result of operation in sagittal synostosis is by means of the cephalic index (breadth of skull/length of skull × 100), as determined on the antero-posterior and lateral roentgenograms. The normal cephalic index is between 70 and 80 and a value less than 70 indicates antero-posterior elongation. As can be seen in table 1, all except two infants in this series had values less than 70 prior to operation, the average index being 65. The degree of abnormality of the index probably reflects the period during intrauterine development at which fusion occurred. Table 1 also indicates

TABLE 1

PARASAGITTAL CRANIECTOMY

Pt.	Age at op.	C.I.*	Interval post-op.	C.I.
1	3 mo.	61	—	—
2	1 mo.	65	4 mo.	74
3	2½ mo.	64	3½ mo.	68
4	2 mo.	71	9 mo.	83
5	6 wk.	63	2 yr.	80
6	2½ mo.	66	2 yr.	75
7	3 mo.	61	6 mo.	66
8	5 mo.	68	3 yr.	64†
9	1 mo.	71	2½ yr.	77
10	3 mo.	67	4 yr.	71
11	2 mo.	58	1 yr.	64
12	5 mo.	67	3 yr.	76
13	6 wk.	63	1½ yr.	77
14	2 wk.	—	1 mo.	70
15	3 mo.	64	—	—
16	5 mo.	68	—	—
17	3 mo.	62	—	—
18	2 mo.	58	1 mo.	63
19	2 mo.	68	2 mo.	74

* CEPHALIC INDEX.

† This patient was one in whom parasagittal craniectomy was performed before adoption of polyethylene film to retard bony union. It seems probable that his craniectomy became functionally closed earlier than suspected by roentgenogram.

the degree of improvement in the cephalic index postoperatively and the period of time during which this improvement occurred (Figs. 3 and 4). It will be noted that all except one patient showed a substantial rise in the index, usually into the normal range.

Of the 19 patients in this series of young infants, five were operated on before the routine placement of polyethylene film over the bone margins to delay regeneration across the artificial suture.[3,5] Of these, three have had repeat craniectomies performed because of regeneration of bone which functionally closed the artificial sutures within a period of 12 to 15 months. One child had three separate operations within the first 2½ years.

The follow-up period varies from a few months to six years. All patients have developed normally and there has been no instance of apparent mental retardation. So far as can be determined no patient has shown any visual impairment. It may be noted that one patient was a twin and there has been no difference in the mental development between the two.

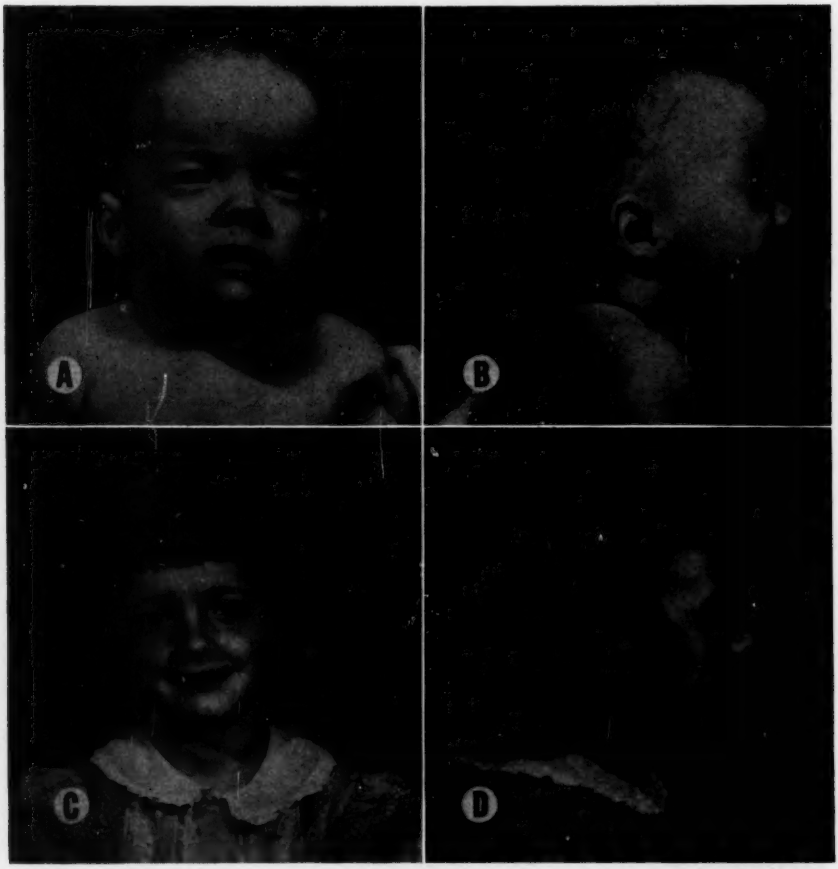


FIG. 3. Premature closure of sagittal suture. A and B: Age 4 mo., prior to parasagittal craniectomy. Note anteroposterior elongation of skull with prominence of occipital portion and high narrow forehead. C and D: Age 5½ yr. Cephalic index rose from 67 to 76 during this interval with normal mental development.

PREMATURE CLOSURE OF CORONAL SUTURE

Not quite so fortunate are those infants in whom the coronal suture is prematurely closed, either unilaterally or bilaterally. Though fewer in number than the patients with sagittal suture fusion alone, their disability is greater and their surgical treatment more complicated. Often there is closure of the squamosal suture and of facial sutures as well. This group of patients also shows a high incidence of associated congenital anomalies, including, in this series, syndactylism, choanal atresia, congenital heart disease, meningocele, cleft palate, micrognathia, congenital ptosis, extraocular palsy and absence of the septum pellucidum.

The frequency of mental retardation in these patients is greater despite early craniectomy than in the sagittal synostosis group. Indeed, in patients with coronal involvement, either

alone or associated with closure of other sutures, pneumoencephalography has been performed on those with apparent retardation of mental development and without exception has shown slight to moderate generalized ventricular dilatation, often accompanied by deep subarachnoidal spaces over the cerebral surface, even during the first 6 months of life. This seems to indicate that either there may be some inherent embryologic defect of the brain which precludes normal development even after the fused sutures are opened or that irreversible structural changes in the brain due to the skull deformity have already

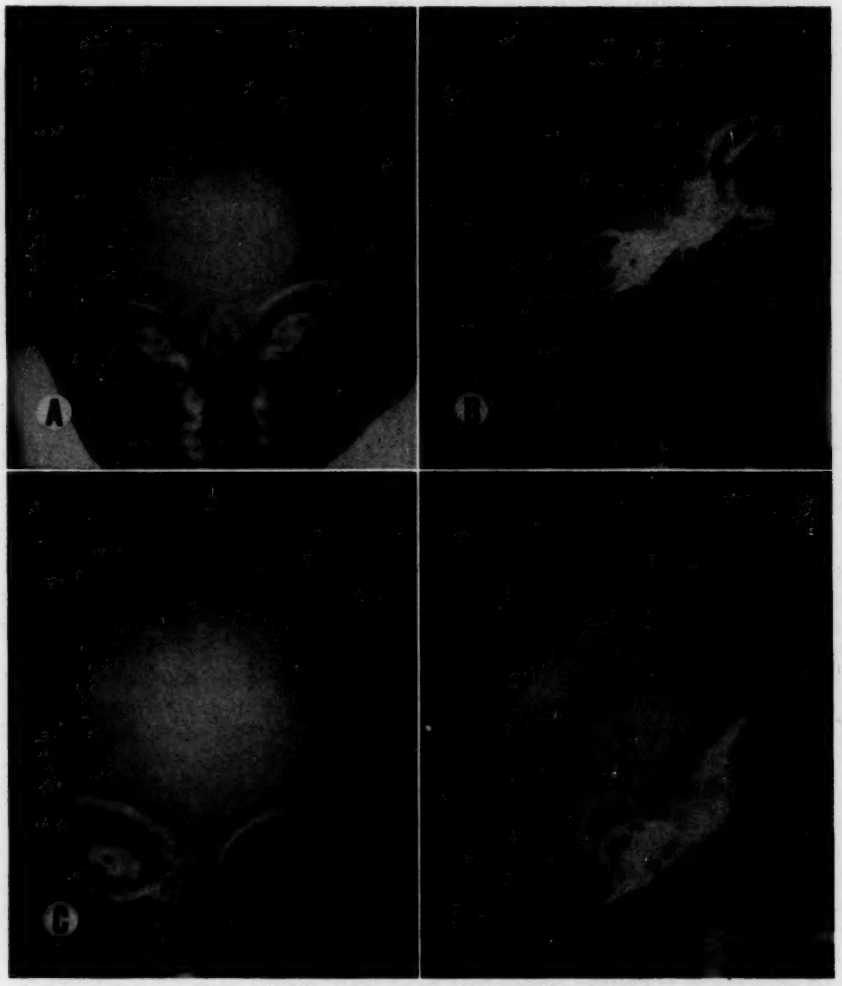


FIG. 4. Premature closure of sagittal suture. A and B: Preoperative RG at 1 mo. of age. Note anteroposterior elongation of skull and increased density of bone along partially obliterated sagittal suture. Cephalic index 65. C and D: Three months following parasagittal craniectomy. Note widening of vault and relative decrease in anteroposterior dimension. Marked widening of craniectomy openings has occurred and new bone is visible within defects. Cephalic index 74.

occurred prior to birth. It is felt, nevertheless, that early operation is necessary in every patient to release whatever growth potential is present.

The principal indication for early treatment of coronal synostosis is prevention of restriction of brain growth and secondary intracranial hypertension. There is no doubt that increased intracranial pressure can result from premature closure of the coronal suture bilaterally although this seldom reaches the point of decompensation until the remaining sutures begin to unite firmly. Generalized increased intracranial pressure in the presence of unilateral coronal involvement has not been noted although there is probably local distortion and constriction of brain growth. Expansion of the previously constricted brain

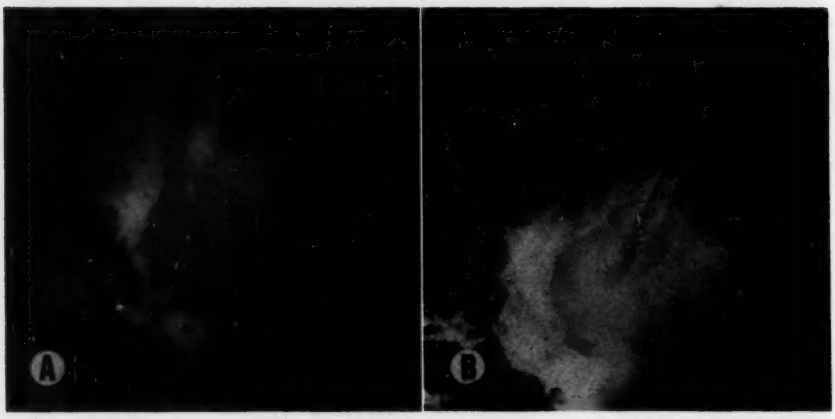


FIG. 5. Premature closure of both coronal sutures. A: RG immediately following bilateral coronal craniectomy at age of 1 mo. Note recession of forehead and narrow anterior fossa. B: RG 8 mo. postoperatively. Note increased size of anterior fossa, marked widening of craniectomy openings and new bone deposition which gives original defect appearance of 2 widely separated defects.

may be inferred from the roentgenographic changes seen during the first few postoperative months; spreading of the craniectomy opening and widening of the narrow anterior fossa as seen in the lateral projection (Fig. 5).

The cephalic index is not as reliable a method of evaluation of skull contour changes following operation for coronal synostosis as it is in the sagittal group. Characteristically patients with coronal suture closure present a broad flat forehead with decreased antero-posterior diameter. This is shown quantitatively in table 2 which reveals that of the 9 patients whose initial roentgenograms are available, all but one had an index of over 80 (upper limit of normal) and 6 of these were greater than 90. Although return to normal limits does not occur postoperatively, the change is invariably toward a lower index. The unreliability of this measuring device in these patients is probably due to the variable tendency toward increasing the height of the cranial vault ("towering") which occurs in some cases to compensate for the diminished antero-posterior expansion.

In the present series, 2 of the 9 patients were thought to be definitely retarded mentally on pre-operative evaluation; both of these had bilateral coronal fusion. Though still below average, these two infants are now progressing in mental development. The remaining patients with coronal suture closure are mentally normal as observed during a follow-up time varying from several months to 4 years. One of these is a twin who has shown no retardation in comparison with her sibling.

Another important reason for surgery within the first few months of life in this group is the prevention of visual loss. Exophthalmos on the involved side renders the eye more susceptible to external trauma, especially with recession of the protective supraorbital ridge. More important than the external deformity, however, is constriction of the foraminae through which pass the optic nerve and nutrient vessels of the eye, and the malformation of the middle fossa.[6] These deformities can be prevented or minimized by early surgery. That an actual change in the basal contour of the skull follows coronal craniectomy can be seen on postoperative roentgenograms (Fig. 5).

If complete fusion of the coronal suture is combined with premature fusion of the

TABLE 2

CORONAL CRANIECTOMY

Pt.	Age at op.	C.I.	Interval post-op.	C.I.
		Bilateral		
1	1 mo.	93	2½ yr.	84
2	6 mo.	97	—	—
3	6 mo.	—	4 yr.	86
4	6 mo.	92	—	—
5	7 wk.	78	5 mo.	76
		Unilateral		
6	5 mo.	93	3 yr.	90
7	5½ mo.	93	1 yr.	88
8	1 mo.	81	—	—
9	2½ mo.	93	10 mo.	90
10	2½ mo.	81	11 mo.	79

orbital bones and deformity of the sphenoid bone bilaterally, resulting in exophthalmos, the following plan of surgical treatment is recommended during the first six months of life. It is wise at this age to divide this treatment into two stages. At the first stage coronal craniectomy is performed on one side in the usual manner. This is carried inferiorly and forward to remove the keel-like inward projection of the lesser wing of the sphenoid bone. It is then easy to penetrate and remove the roof and lateral wall of the orbit widely. The dura of the under-surface of the frontal lobe and apex of the temporal lobe, as well as the capsule of the orbit, should be left intact to avoid postoperative pulsating exophthalmos. The coronal craniectomy margins are covered with polyethylene film and the incision closed. Inasmuch as coronal synostosis is often accompanied by choanal atresia and congenital deformity of the nasopharynx, there is some advantage in keeping these infants in a moist atmosphere following endotracheal intubation to decrease postoperative edema of the larynx. Five to 10 days later, depending on the infant's general condition, the coronal incision is reopened and the same procedure carried out on the other side. The necessity for scrupulous care of the eyes during the postoperative period is obvious.

Although in many of the present cases insufficient time for follow-up has elapsed, there has been no indication of visual impairment in any patient treated in this manner. Optic nerve pallor has not been noted in any patient preoperatively or on subsequent examination.

The third reason for emphasizing the earliest possible treatment of coronal craniosynostosis is the cosmetic improvement which follows surgery. The deformity is characterized

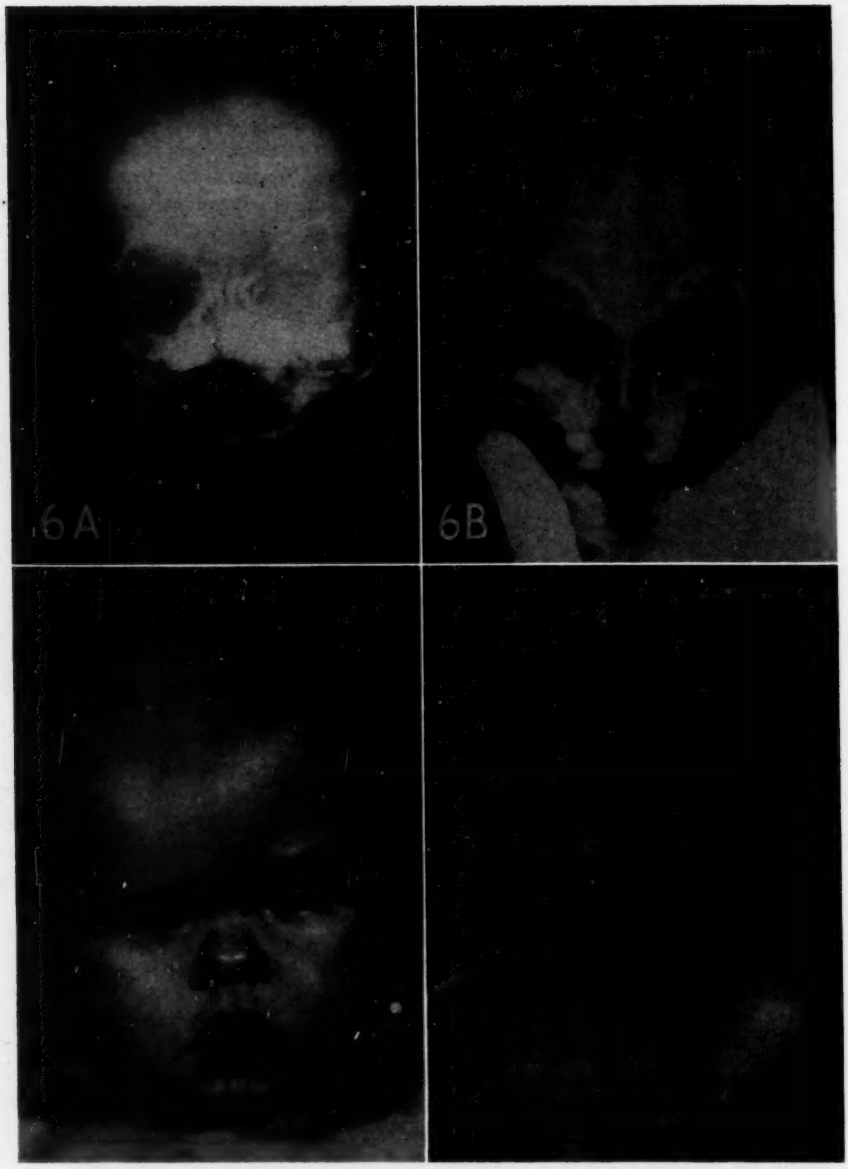


FIG. 6. Premature closure of L coronal suture. A: Preoperative RG at 5 mo. of age showing deformity of orbit and sphenoid wing and enlarged temporal fossa. (Curvilinear density over L side of head is artefact caused by head-holding apparatus.) B: RG 8 mo. following L coronal craniectomy and orbital decompression. Note symmetry of orbits and temporal fossae.

FIG. 7. Premature closure of L coronal suture. A: Age 5 mo. Note deformity of L supraorbital ridge and flattening of L forehead. B: Age 1½ yr. Note almost complete disappearance of asymmetry following coronal craniectomy and orbital decompression.

by depression of the supraorbital ridge on the involved side with flattening of this side of the forehead. This part of the facial deformity can be corrected almost completely by operation within the first few months (Figs. 6 and 7). Some of the facial deformity, however, is often caused by defective development of the facial bones themselves so that there may be persistent asymmetry or deformity in spite of early operation.

Of the 10 cases of craniosynostosis involving the coronal sutures only one was operated on before the use of polyethylene film to cover the bone edges. This patient required reoperation after two years because of regeneration of bone and functional closure of the artificial suture. One other patient in whom film was used at the original operation performed at one month of age has required reoperation after a year. The remaining patients have maintained functionally open craniectomies for a sufficiently long time to obviate the need for further surgery.

A word of caution should be added concerning the necessity for extension of coronal craniectomy beyond the squamosal suture. Because of the marked deepening of the middle fossa which may be present, there is a tendency to underestimate the distance from the fontanelle to the squamosal suture. This suture line should be clearly visualized to determine its patency, which may be questionable by roentgenogram. If it is found to be patent the coronal opening should be extended across it for a distance of at least 1 cm. If, however, fusion of this suture has also occurred subtemporal decompression or extension of the craniectomy posteriorly along the fused squamosal suture line is indicated.

Premature Closure of Multiple Sutures

The greatest urgency for early treatment occurs in the group of infants in whom there is combined coronal and sagittal synostosis. These patients are particularly subject to restriction of brain growth and increased intracranial pressure at an early age. It is important, of course, to distinguish this type of patient from the primary microcephalic infant. In the latter the suture lines are present by roentgen examination, though not as prominent as normal because of the lack of expanding force from within the cranial vault. It should always be possible to make the correct diagnosis by roentgen examination if good films are obtained and the radiologist is familiar with the condition.

Of the three patients with sagittal and coronal involvement in this group of young infants one had unilateral coronal fusion and the other two bilateral coronal fusion. These three infants have had multiple stage operations which have resulted in considerable improvement in appearance as well as fairly normal mental development. This is in marked contrast to similar treatment in older children in whom the improvement in mental development and appearance is much less striking.

The most severe cranial deformity of the present series occurred in a female infant who was operated on first at 1½ weeks of age. Subsequently repeated craniectomies, sagittal and coronal, and orbital decompressions were performed to maintain functional patency of the cranial sutures. Although the child is by no means normal in appearance there has been a striking improvement in the outward contour of the severely deformed skull. She has been definitely retarded in mental development but is steadily progressing and is able to walk and say a few words at 20 months (Fig. 8). Another patient in this group demonstrated the strong tendency of the skull and brain to assume normal contour by exhibiting marked change in the shape of the head during the actual operative procedure which was performed at 2 weeks of age. This patient has subsequently shown normal mental develop-

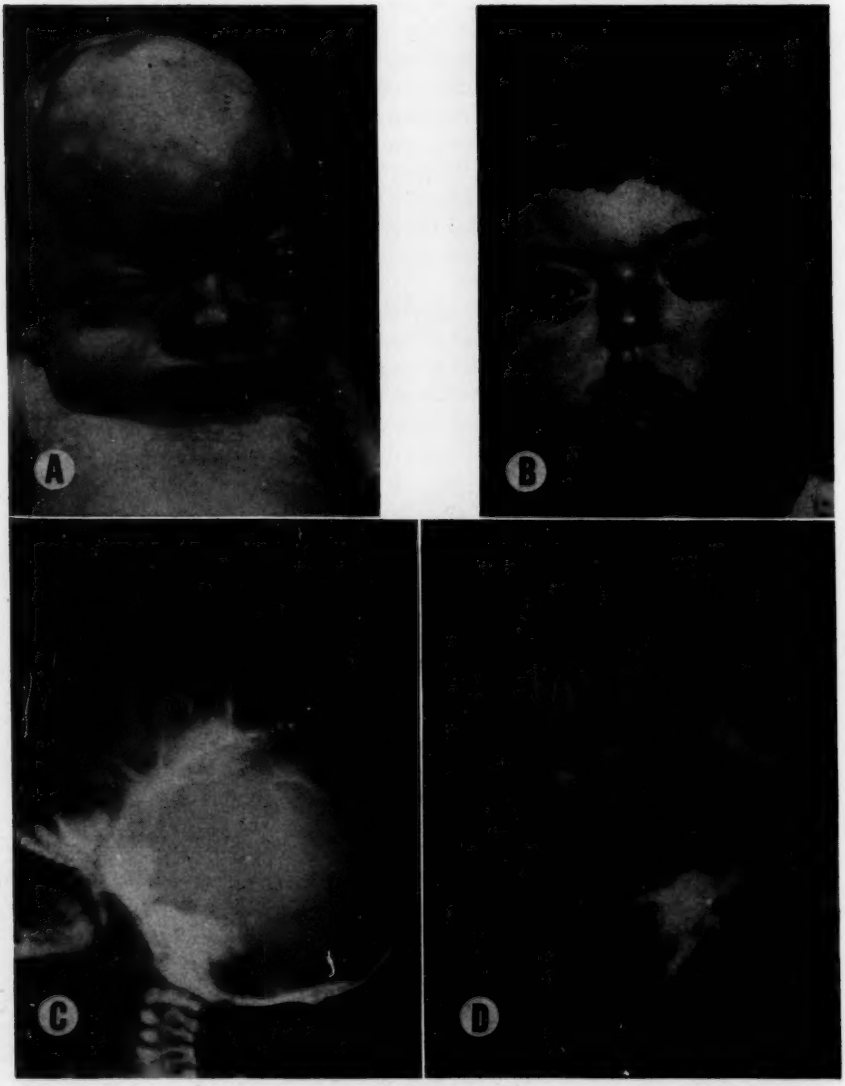


FIG. 8. Premature closure of sagittal and both coronal sutures. A and C: Age 10 days, prior to operation. Note marked orbital and facial deformity and complete fusion of coronal sutures. Five separate operations were performed during 1st 14 mo.: bilateral coronal craniectomy, parasagittal craniectomy and L orbital decompression, R orbital decompression, repeat coronal craniectomy, and repeat parasagittal craniectomy. B and D: Age 2½ yr. showing improvement in appearance of face and skull. Note residual towering of cranial vault and foreshortened anterior fossa.

ment (Fig. 9). None of the three patients with sagittal and coronal suture fusion has any known visual impairment.

Two patients had combined coronal and lambdoid fusion. That this may constitute an urgent situation because of intracranial hypertension is evidenced by the fact that one of these had papilledema at 2 months of age, the only patient in the entire series who showed this sign. This patient's cephalic index dropped from 90 to 85 during the first postoperative month and there was marked spread of the artificial sutures.

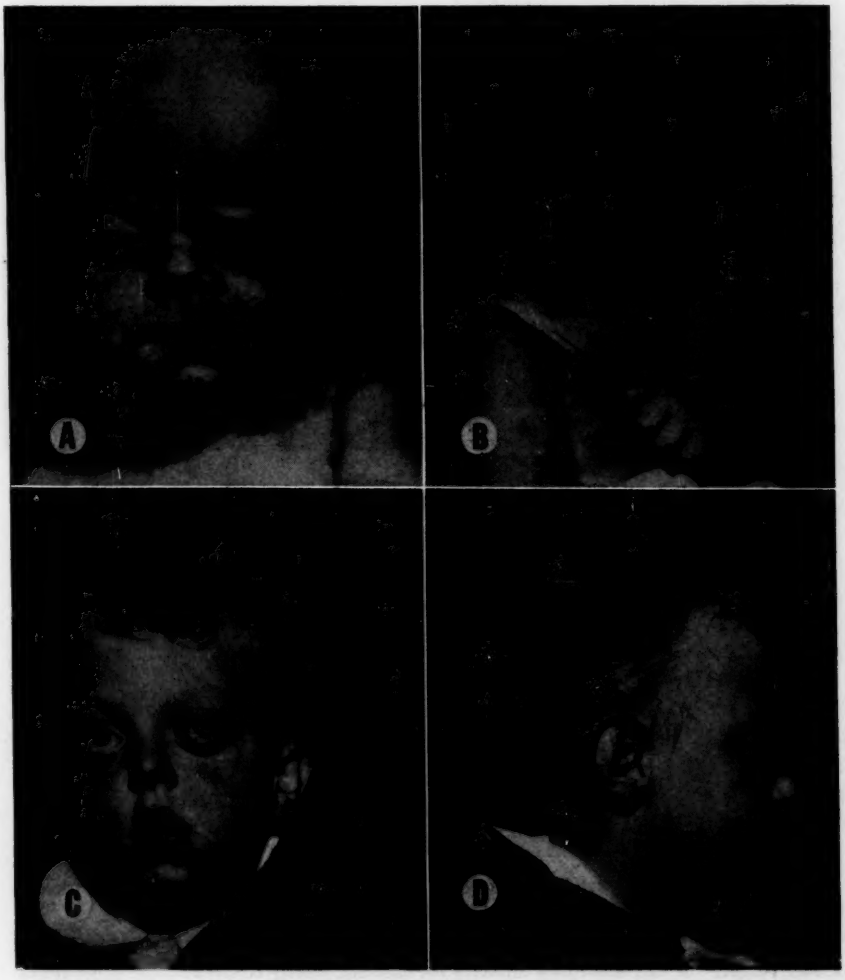


FIG. 9. Premature closure of sagittal and R coronal sutures. A and B: Age 2 wk., prior to parasagittal and R coronal craniectomy. Note asymmetry of skull with orbital deformity on R and depression along synostosed coronal suture. Because of inadequate anteroposterior growth following initial operation bilateral coronal craniectomies were performed at age 7 mo. C and D: Age 3 yr., showing improvement in shape of skull with residual "towering." Orbital deformity on R is still apparent.

Miscellaneous

One of the miscellaneous patients presented the unique problem of closing the widely gaping metopic suture which accompanied coronal synostosis and severe orbito-facial deformity. This was accomplished at 4½ months of age by entirely detaching the frontal bone plates on each side of the metopic suture, sliding them together, and fixing them in the midline. This maneuver shifted the defect from the midfrontal region to the temporal areas. Bilateral orbital decompressions were also done because of the deformity of the orbital bones. The cosmetic improvement has been gratifying. In addition to the cranial deformity this child has syndactylism of all extremities and is mentally retarded though now progressing consistently; vision is apparently normal (Fig. 10).

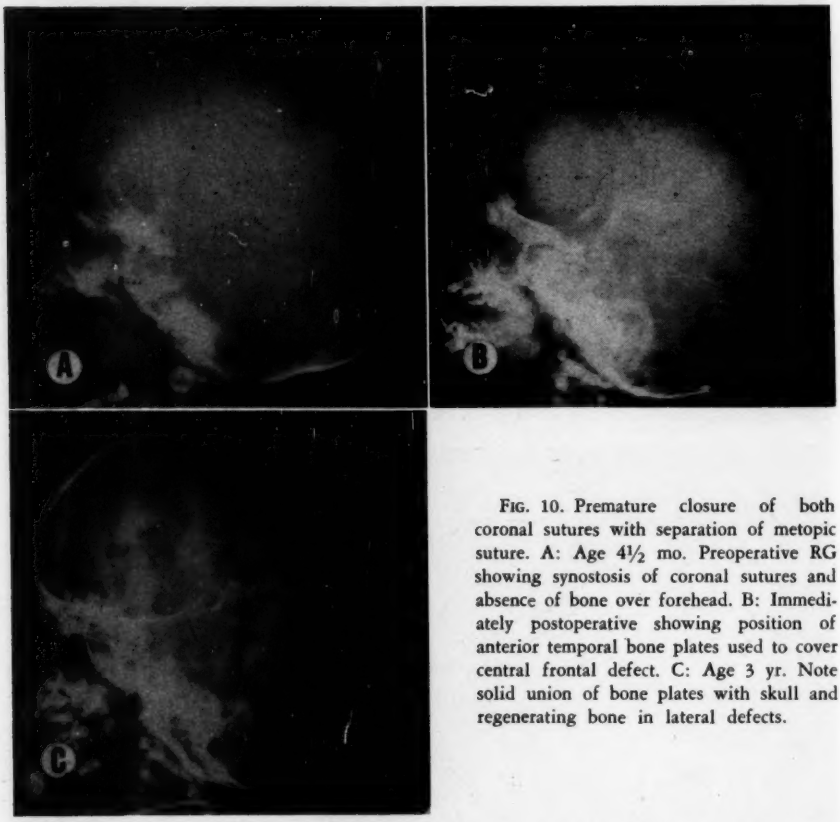


Fig. 10. Premature closure of both coronal sutures with separation of metopic suture. A: Age 4½ mo. Preoperative RG showing synostosis of coronal sutures and absence of bone over forehead. B: Immediately postoperative showing position of anterior temporal bone plates used to cover central frontal defect. C: Age 3 yr. Note solid union of bone plates with skull and regenerating bone in lateral defects.

The other case included in this group is one of premature closure of the metopic suture alone. Surgery for this deformity is purely for cosmetic improvement as there is no indication that restriction of brain growth occurs.

Discussion

Although some observers still feel that there is no urgency about operation for craniosynostosis, the outcome in these patients in whom surgery was performed within the first

few months, compared to those with similar lesions treated later in life, has led the authors to the conviction that early recognition and treatment is of extreme importance. This is prophylactic rather than curative surgical treatment. The authors believe that if one waits until such signs as mental retardation, visual impairment or persistent headache can be evaluated accurately, valuable time has been lost and irreversible brain damage done. Moreover, the significance of the patient's appearance with deformity due to craniosynostosis should not be underestimated; the best cosmetic results can always be obtained by early operation.

This report is concerned only with patients in whom operation was undertaken at less than 6 months of age. This is an arbitrary selection and should not be construed to mean that there is equal opportunity for correcting the deformity throughout this period. It must be remembered that the brain normally doubles in weight during the first seven months and the earliest possible treatment, therefore, allows the greatest advantage. There is no contraindication to surgery within the first month of life as soon as the infant has become reasonably stable physiologically. Of the 36 patients reported here, 24 were operated on within the first three months and eight within the first month. The youngest was 1½ weeks of age.

Any operation for craniosynostosis in infancy is merely a delaying procedure. The aim is to provide artificial sutures which will remain patent during the period of maximum brain growth. Polyethylene film placed over the craniectomy margins has greatly facilitated this purpose. As new bone forms from the dura (endostium) within the defect, the original craniectomy may come to appear like two separate defects since this strip of new bone is prevented by the film from fusing with the skull on either side (Fig. 5). If the defect becomes bridged clinically and by roentgenogram and if the head has ceased to grow by careful measurements during the first three years, craniectomy should be repeated.

Several technical problems of importance to craniectomy in young infants should be emphasized:

1. Blood loss during and after operation, because of extensive scalp reflection, periosteal stripping and bone removal, is unusually large in proportion to the size of the patient. Transfusion should be started at the beginning of operation and given liberally throughout the procedure. Hemoglobin and red cell counts are made early in the postoperative period and must be checked repeatedly if subgaleal accumulation of blood occurs.

2. Following craniectomy in this young group there is enough immediate expansion of the skull to make careful attention to the head dressing mandatory. The dressing must never be applied tightly as is so often the temptation to prevent subgaleal fluid collection. The infant's scalp over areas of prominence is extremely susceptible to pressure, and ischemic necrosis may result from postoperative scalp edema and enlargement of the cranial vault beneath the dressing. In the present series there were two such complications.

3. The third problem concerns infection. Wide stripping of periosteum almost invariably leads to postoperative subgaleal fluid and blood accumulation. This should be aspirated under the most careful sterile precautions. Because of the use of polyethylene film it was considered unwise to leave a drain in the subgaleal space postoperatively. If subgaleal infection should occur the film must be removed immediately to facilitate treatment of the infection and reduce the possibility of osteomyelitis. One such infection occurred in this series but was promptly brought under control after removal of the polyethylene film.

Summary

One hundred and twenty children have been treated surgically for premature fusion of the cranial sutures in this clinic.

Thirty-six of these have been operated on in the first six months of life and constitute the material on which this report is based. These have included 19 instances of sagittal suture closure, 10 of coronal closure, 5 of multiple suture involvement and 2 miscellaneous cases.

The marked reduction in incidence and degree of mental retardation, the prevention of visual impairment, and the improvement in cosmetic appearance which can be achieved by recognition and surgical treatment of this lesion in early infancy are emphasized.

The operation of choice in this clinic is linear craniectomy parallel to the suture which is prematurely fused with insertion of polyethylene film over the bony margins to delay closure.

With proper precautions and supportive treatment this type of surgery is well tolerated and the complications are negligible during the first few months of life.

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Spanish Abstract

Importancia del Tratamiento Quirúrgico Precoz de la Craneosinostosis; Revisión de 36 Casos Tratados Durante los Primeros Seis Meses de la Vida

Existen dos razones principales por las cuales el tratamiento quirúrgico de estos enfermos no es satisfactorio, una es el error de no diferenciar los casos de microcefalia primitiva para los que la intervención quirúrgica no da beneficio alguno y la otra es no reconocer y tratar la craneosinostosis lo suficientemente temprano para prevenir la lesión cerebral irreversible, la pérdida de la visión y las deformidades craneanas en grado extremo. Pocos son los casos reportados que han sido intervenidos quirúrgicamente en la época de crecimiento rápido cerebral, aunque en general los cirujanos están de acuerdo en operar lo mas pronto posible y esto se debe a que muy a menudo el diagnóstico correcto se hace tardíamente.

De los 120 enfermos operados de craneosinostosis, 36 o sea 1/3 aproximadamente han sido tratados durante los primeros 6 meses de la vida. Sus tipos fueron los siguientes: 19 con fusión prematura exclusiva de la sutura sagital; 10 con cierre de la coronal, 5 unilateral y 5 bilateral habiendose encontrado también fusión de la escamosa en 4 de estos pacientes; 5 con fusión de dos o mas suturas, 3 de la coronal y sagital y 2 de la coronal y lambdoidea y finalmente 2 casos más; uno con fusión bilateral de la coronal y sagital pero con persistencia de la metópica y el otro con fusión de ésta sutura exclusivamente.

Cierre Prematuro de la Sutura Sagital

En esta variedad no se presenta generalmente hipertensión intracraneana de significación hasta cerca de los dos años de edad, cuando se hace el cierre funcional de las otras suturas existiendo

hasta entonces una separación compensadora de la sutura coronal y lambdoidea en respuesta al crecimiento cerebral lo cual da la elongación anormal del craneo. Otra prueba de la hipertensión intracraneana es la separación de las suturas quirúrgicas durante las primeras semanas o meses después de la operación.

De los 19 enfermos de este tipo, 5 se operaron antes de que se usara como rutina la película de polietileno entre los márgenes óseos para retardar la regeneración ósea a través de la sutura quirúrgica. De estos, 3 requirieron craniectomias repetidas por cierre funcional de las suturas artificiales debido a regeneración osea, en un lapso de 12 a 15 meses. Uno de ellos tuvo 3 operaciones en 2½ años.

El período postoperatorio de observación varió desde unos meses hasta 6 años; con excepción de un solo enfermo todos los demas mostraron un aumento substancial de su índice cefálico, alcanzando generalmente sus límites normales. Todos se desarrollaron normalmente y no hay un solo caso aparente de retardo mental, y hasta donde puede decirse no hay ninguno que muestre dificultad visual. Uno de los enfermos es gemelo y no ha habido diferencia en el desarrollo mental de ambos niños.

Cierre Prematuro de la Sutura Coronal

En este grupo, desgraciadamente los resultados no son tan afortunados debido a fusión simultánea de la escamosa y de las suturas de la cara, a la frecuencia de malformaciones congénitas asociadas como sindactilia, atresia de las coanas, cardiopatías, meningocele, etc. así como de retardo mental aún en los casos operados tempranamente. Tal parece como si existiera un defecto embriológico del cerebro que impidiera su desarrollo normal aún después de que las suturas fusionadas han sido abiertas, o que han ocurrido alteraciones estructurales cerebrales irreversibles antes del nacimiento debidas a deformidad del cráneo, sin embargo, se piensa que la operación precoz es necesaria en cada enfermo para permitir el crecimiento potencial que esté presente y evitar la hipertensión intracraneana secundaria que sin duda ocurre en los casos de fusión bilateral aunque raramente alcanza el grado de descompensación sino hasta que las suturas restantes comienzan a unirse firmemente. Otra razón importante para intervenir tempranamente es la conservación de la agudeza visual y finalmente evitar o hacer mínima la deformidad externa aun cuando sea por fusión unilateral. El exoftalmos y la constricción de los canales ópticos a través de los cuales pasa el nervio y vasos nutricios del ojo, y la deformación de la fosa cerebral media también son evitados o disminuidos al máximo.

En este grupo, 2 de los enfermos con fusión bilateral eran francamente retardados mentales en su evaluación preoperatoria y aunque aún siguen siéndolo están progresando en su desarrollo mental. El resto de los pacientes tenían mentalidad normal durante el lapso de observación que varió de unos meses hasta 4 años. En ninguno se ha visto disminución de la agudeza visual. De los 10 enfermos, 9 se operaron usando la película de polietileno y de estos uno solo ha necesitado reoperarse después de un año.

Cierre Prematuro de Múltiples Suturas

La necesidad mas urgente de tratamiento precoz la representan la sinostosis combinada de la sutura coronal y sagital pues sufren tempranamente de gran restricción del crecimiento cerebral y de hipertensión intracranenana, y son los casos mas importantes de distinguir de la microcefalia primitiva, lo cual es posible por medio de los rayos X ya que dichas suturas están presentes aunque no son tan prominentes como en el cráneo normal por falta de fuerza de expansión dentro de la bóveda craneana. Fueron 3 los casos de esta variedad de sinostosis, uno solo con fusión unilateral de la sutura coronal; todos requirieron múltiples operaciones en etapas pero se lograron mejorías estéticas considerables y un desarrollo mental bastante normal en contraste con los resultados obtenidos en niños mayores. Ninguno ha mostrado lesión visual.

Otros 2 casos tenían fusión de la sutura coroniana y lambdoidea, uno de ellos con papiledema a los 2 meses de edad, único en todas las series de enfermos, lo cual evidencia hasta la elocuencia la urgente necesidad de operar muy tempranamente.

Miscelaneos.—Fueron dos casos, uno con sinostosis de la sutura coronal con amplia abertura de la metópica y el otro con sinostosis aislada de la metópica.

Los autores insisten finalmente en la precocidad del tratamiento quirúrgico y no esperar según algunos observadores hasta evaluar con precisión el retardo mental, la disminución visual, o la

cefalea, pues para entonces ya se ha hecho una lesión cerebral irreversible, además de que los resultados estéticos mejores se obtienen con tratamiento temprano. La edad mas oportuna es la mas temprana tan pronto como el lactante se ha estabilizado fisiológicamente y puesto que se sabe que el cerebro dobla su peso durante los primeros 7 meses, entre mas temprano se haga la intervención es mejor, no habiendo contraindicación de operar durante el primer mes. De los 36 enfermos de la serie, 24 se operaron antes de los 3 meses y 8 durante el primer mes y la mas precoz a los 10 días. La placa de polietileno sobre la craniectomía simplifica mucho el proveer una sutura artificial que permanezca permeable durante el período de máximo crecimiento cerebral; si esta se une clínicamente y a los rayos X, y la cabeza deja de crecer durante los primeros 3 años, debe repetirse la craniectomía.

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AMINO ACID METABOLISM IN PATIENTS WITH ACUTE LEUKEMIA

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THE mechanism responsible for the dysplastic cellular pattern which characterizes the bone marrow of patients with acute leukemia is not known at present. Disordered metabolic processes within the developing cell may reflect inactive or improperly functioning specific enzyme systems that are concerned in the maturation of individual cells. According to this concept the bone marrow cells may "grow off on a tangent" and accumulate in sufficient numbers so that the marrow smear often reveals nearly complete replacement by "blast" cells. These forms cannot resume their normal developmental pattern.

The clinical and bone marrow remissions in individual patients induced by administration of folic acid or citrovorum antagonists provided an opportunity for controlled metabolic observations in the same patients before and after therapy. A previous report from this laboratory[1] described long term clinical observations on cases of acute leukemia treated in this manner. In this communication we wish to report some results of certain biochemical changes that accompany the dysplastic process and specifically the changes in amino acid metabolism.

A. FREE AMINO ACIDS

Experimental: Free amino acids in the plasma of normal subjects and of patients with acute leukemia were determined according to the microbiologic method described by Henderson, Brickson and Snell.[2] Blood obtained from the patient was mixed with dry potassium oxalate and centrifuged in order to obtain the plasma. Approximately 15 cc. of blood was withdrawn in order to have enough sample to analyze for essential amino acids. Preparation of the protein-free plasma filtrate was made according to the method of Hier and Bergeim[3] and was kept frozen until analyzed. The uniform medium of Henderson and Snell was used with the appropriate bacteria necessary to determine the individual amino acids.[4] The micro-adaptation of the microbiologic method used was that of Henderson et al.[5] This method was facilitated by a Cannon pressure regulating device† attached to a dispensing apparatus which dispenses measured minute quantities of protein-free filtrate so that the final volume of incubating medium was 0.2 ml. A concentric glass electrode titrating mechanism attached to a galvanometer provided the quantitative estimation of the acid produced in the incubated tubes.[6]

The patients with acute leukemia studied were those under the authors' care in the pediatric ward and in the outpatient clinics of the University of Illinois Research and Educational Hospitals.[1] Many of these children had several amino acid analyses during the course of the disease. One determination was usually performed when the diagnosis was made, and additional analyses were

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TABLE 1

FREE AMINO ACIDS IN PLASMA OF NORMAL INDIVIDUALS AND IN PATIENTS WITH LEUKEMIA
(mg./100 cc. plasma)

Amino Acids	Control	Before Remission	In Remission
Histidine	10.9 (17)	11.5 (39)	11.1 (17)
Arginine	10.4 (11)	14.3 (33)	11.5 (17)
Methionine	3.6 (13)	4.4 (30)	5.7 (10)
		35–48†	17–143 (4)†
Tryptophane	7.8 (14)	7.7 (32)	9.5 (12)
*Valine[1]	23.7 (20)	29.1 (36)	29.4 (16)
*Phenylalanine[2]	7.1 (20)	18.9 (35)	19.3 (18)
Leucine	15.1 (17)	20.1 (40)	19.0 (17)
*Tyrosine[3]	9.3 (17)	15.0 (35)	18.9 (15)
*Isoleucine[4]	7.1 (11)	11.5 (39)	10.7 (18)
Threonine	14.1 (10)	15.1 (31)	15.4 (18)
Lysine	24.1 (10)	15.1 (31)	15.4 (18)
Glutamic Acid		52.7 (32)	49.6 (12)

* Denotes significant differences.
† Values not included in means
(Number of bloods analyzed—in parentheses)
[1] $F=14.81$ Snedecor,[6] p. 249.
[2] $t_{48}=6.08$.
[3] $t_{48}=3.05$.
[4] $t_{55}=3.21$.

accomplished at intervals during antagonist therapy and subsequent follow-up. Preliminary observations indicated that the amino acid levels of the fasting patient were not appreciably different from those obtained from patients after feeding. While most values are from fasting samples, a few are from specimens obtained 2 to 4 hours postprandially.

Results: Amino acid levels in protein-free filtrates obtained from whole blood of normal individuals and from patients with leukemia are listed in table 1 in mg./100 cc. The figures in parentheses represent the number of determinations. From these data it may be observed that significant differences* were obtained for tyrosine, phenylalanine and isoleucine. The average tyrosine level of "normal" patients was 9.3 as compared to 15.0 mg./100 cc. in the leukemic group. The phenylalanine values of 7.1 in the control compared significantly with 18.9 in the leukemic group. No significant difference was observed between patients who were in remission or who were in the initial phase of the disease process. The values for valine determinations indicate that the difference between the means is not significant but the differences between the variances is highly significant.[6] Thus, patients with leukemia show more variable valine values than do the controls. The mean values for isoleucine indicate that 7.1 mg. in the control group is significantly different when compared to the 11.5 mg. in the patient with leukemia. There is again no difference between values obtained before and after remission.

Two patients with leukemia had extremely high levels of methionine, ranging from 17 to 143 mg., for which no explanation can be given at the present time. One of these patients, T.B., who was lost from the authors' care for a period of 4 mo., returned to this hospital prior to his death and at that time methionine values were normal after a long period of remission. Terminally the bone marrow was in relapse, but there was no rise in free methionine in the blood at that time.

Histidine, arginine, tryptophane, leucine, threonine, lysine and glutamic acid levels were not significantly different in the patients with leukemia when compared to normal individuals of the same age.

* Aid in statistical evaluation was provided by Dr. E. Becker.

B. Tyrosine Excretion Studies

Experimental: Twenty-four hour samples of urine were collected on all patients with leukemia prior to therapy and after the administration of folic acid antagonists. The urine was preserved with toluol and brought to the laboratory after the completion of the 24 hr. sample. In infants the gathering of the daily urine was divided into 3 equal 8 hr. periods to facilitate collections, the samples being pooled at the end of the 24 hr. Several considerations in the evaluation of tyrosine excretion are: (1) the age of the patient; (2) height and weight, and therefore, perhaps, surface area; and (3) the diet during the time the urine was collected. However, all these considerations were in part minimized by the fact that each patient served as his own control while receiving a constant diet. The method for determining "tyrosyl" compounds was that of Medes.[7] This method determines most of the phenolic groups and is not specific for tyrosine, but represents precursors and metabolic products from tyrosine and phenylalanine.

Results: More than 175 individual urines were studied from patients with leukemia, normal individuals and from several hospitalized patients who did not have leukemia. No dietary restrictions were in effect and the purpose was to compare relative "tyrosyl" excretion. Eighteen patients with acute leukemia averaged 137.1 mg. of urinary "tyrosyl" in 24 hr. as compared to 115.8 mg. for normal individuals of the same age group. In order to determine if the urinary volume had any influence on excretion of these compounds, table 2 also lists the average excretion as 0.32 mg./cc. urine in normals and 0.23 mg./cc. in the patients with leukemia. These values are similar and it is apparent that the phenolic compounds present in the urine and determined as "tyrosyl" do not reflect a metabolic change in this disease. In this connection it is of interest to recall that increased quantities of hydroxyphenol compounds have been found in patients with pernicious anemia,[8,9] with acute yellow atrophy, and with other degenerative hepatic conditions.[10] Evidently the invasion of the liver or other organs by the leukemic process does not disturb those mechanisms which form "tyrosyl" compounds. Further discussion on this point will be found below.

TABLE 2

Urinary "Tyrosyl" Excretion of Normal Individuals and in Patients with Leukemia

	Average	
	Mg. Tyrosyl/24 hr.	Mg. Tyrosyl/cc. urine
12 Normal	115.8	0.32
18 Leukemic	137.1	0.23

C. Creatin Excretion Studies

Experimental: The 24 hr. urine samples were analyzed for creatine and creatinine[11] in order to assess further if metabolic processes were accelerated sufficiently to affect protein catabolism. If proteins were readily broken down in patients with leukemia, then creatine/creatinine values should be higher than in normal patients on similar diets. While the degree of liver involvement could not be accurately assessed in the individual patient, the ability of this organ to metabolize creatine would also be reflected in the creatine/creatinine values.

Results: The creatine and creatinine values in the urine of patients with leukemia and normal individuals, together with the creatine/creatinine ratios, were highly variable in both groups at all ages. The creatine and creatinine values in the patients with leukemia were not different from normal individuals or from hospitalized patients without liver or muscle disease, and no purpose would be served in presenting approximately 150 variable values in table form. From these values it is implied that the ability of the liver to metabolize creatine or its precursors is retained in large measure in spite of the leukemic process. Neither muscle wasting nor decrease in body weight appears to contribute to increased creatinine excretion. The influence of the anti-folic acid compounds is apparently not reflected in the creatine/creatinine excretion.

Discussion

In the past few years an increasing amount of information has become available on the role of amino acids and proteins in general body processes. It has been demonstrated that depleted protein reserves result in loss of amino acids and are paralleled by a concomitant tissue loss of certain vitamins and enzymes. It might, therefore, be anticipated that amino acid and protein metabolism would be abnormal in leukemia. The specific role which amino acids and proteins play in the development of the leukemic cell has not been accurately defined, however. Becher and Herrmann[12] had found earlier that a protein-free filtrate of the blood of patients with leukemia contained higher concentrations of total amino acids than did normal individuals, but no quantitative comparisons for the specific amino acids were made. Okada and Hayashi[13] reported two amino acid nitrogen values in chronic myeloid leukemia but did not compare these with figures from normal individuals.

The data in this report provide quantitative information for individual free amino acids as they occur in the plasma of patients with leukemia. The findings of elevated tyrosine and phenylalanine in the blood of patients receiving a folic acid antagonist are of special interest because of the observations made in this laboratory[14] on the hyperpigmentation of the skin in patients receiving these drugs for long periods. The higher circulating phenylalanine and tyrosine levels in the plasma imply that these amino acids were available for melanogenesis in antagonist-treated patients but not in patients receiving no folic acid antagonists. However, this is a dubious explanation since no evidence is available to indicate that the higher level *per se* has any mass action effect on a particular structure or function such as the deposition of melanin in the skin. In this connection it might be mentioned that patients with phenylpyruvic oligophrenia having high phenylalanine blood values show no increase in skin pigmentation. The interconvertibility of tyrosine and phenylalanine presumes that the elevation of one amino acid would make available either compound on demand for some metabolic process. The histopathologic evidence previously reported[14] together with the elevated phenylalanine and tyrosine levels in the plasma provide indirect evidence that the folic acid antagonists play some role in increased melanin formation in the treated patients. Since hyperpigmentation has been observed in some cases of chronic disease, aminopterin may accelerate the process by interfering with normal inhibitors of melanin formation in white skin. Several of these inhibitors are closely related to the sulfur-containing amino acids and exert their effect by binding the copper which is necessary for tyrosinase action. Lerner and Fitzpatrick[15] have reviewed the group of substances which inhibit the copper-containing tyrosinases.

At the present time the fact that the blood tyrosine and blood phenylalanine levels are high makes interpretation of the tyrosine excretion in the urine a difficult one. It may be supposed that if these amino acids were circulating in the blood at increased levels they might also possibly be excreted in the urine and be represented as "tyrosyl" compounds. However, if they are concerned in melanin formation one would suspect that they would be rapidly utilized and therefore would not appear in the urine. It seems therefore that tyrosine excretion in the urine does not provide conclusive information.

Of distinct interest are the findings that isoleucine and occasionally valine show high plasma values in patients with leukemia. There is very little to suggest that isoleucine or valine are concerned with any known aberration in the leukemic process or are really concerned in any known enzyme system in normal patients. While such systems may be found in the future, there is no explanation for the higher value of these amino acids in patients with acute leukemia at the present time.

Although two of the authors' patients had unusually high methionine levels, the clinical findings in these patients were identical with all the others studied. A suggested relationship between methionine and leukemic process is one which recognizes that methionine is a "methyl donor" and that folic acid and vitamin B_{12} play important roles in the transmethylation process.[16] Together with vitamin B_{12}, folic acid may be closely related metabolically to methionine, choline or choline oxidase[17] and these compounds may have some mutual interdependence for the formation of some specific bone marrow substance. The coenzymes concerned in transmethylation processes may very well function in the formation of specific constituents of bone marrow cells.

Allen and his workers[18] have suggested that the so-called "high protamine titration" value which theoretically exists in patients with bleeding tendencies such as leukemia may be due to a hyperheparinemia which can be counteracted by toluidine blue and protamine. Since these are basic compounds containing amino groups it is of interest to note that the present authors' values for lysine in the plasma indicate normal basic amino acid levels in patients receiving folic acid antagonists or in untreated patients with leukemia. While hyperheparinemia has been proposed as a partial explanation for bleeding tendencies, Freeman and Hyde[19] have indicated that unknown anticoagulants or some mucopolysaccharides are more likely substances concerned in coagulation.

Creatine and creatinine values in the urine of patients with acute leukemia were entirely normal, indicating that the role of the liver and the role of the muscle mass in metabolizing creatine and its by-product is not greatly affected in acute leukemia. It appears unlikely from the creatine determinations in patients with leukemia reported here that unusual creatine synthesis occurs endogenously from protein breakdown. Since the urinary creatine values were not different from normal, it is in marked contrast to the elevated creatine excretion found in leukemic mice.[20] Dinning and Day[21] also reported that when aminopterin was withdrawn there was marked creatinuria coincidental with white blood cell increase. Additional critical information is necessary to delineate whether increased excretion of creatine in mice represents synthesis by the body or increased breakdown of such creatine precursors as arginine, glycine and methionine.

These considerations are closely related to the findings of Baldridge and Barer[22] who established that protein catabolism was directly related to the increased oxygen consumption and was responsible for the increased basal metabolic rate observed in patients with leukemia by earlier workers.[23-26]

The role of proteins and amino acids in cellular metabolism is paralleled by the influence of some vitamins which act as coenzymes in the processes of protein synthesis. Closely related are the coenzymes which form nucleic acids and nucleoprotein precursors. It has now been established that folic acid and citrovorum factor are necessary for the formation of purines and other nucleic acids precursors,[27, 28] but it is not known whether the "blast" cells in patients with leukemia have an abnormal amount or an abnormal kind of nuclear material within the immature cell. However, it is known that the accumulated leukemic cells in the marrow have a high folic acid and citrovorum factor content[29] and this may be indirect evidence that these cells probably have an unusual quantity of nucleic acids or their precursors. Additional evidence that cell division and the formation of certain desoxyribonucleic acids are parallel is provided by the work of Goldthwait and Bendich.[30] These workers showed that the incorporation of formate ion into desoxyribonucleic acid could be inhibited by aminopterin, so that "there is a remarkable parallel between the decrease in formate incorporation into thymine and into purines produced by aminopterin." This action assumes greater significance in a discussion of leukemia since the vitamin

antagonists may induce temporary clinical remission not by producing a folic acid deficiency *per se* but by preventing the formation of abnormal cells which are due to an aberration in the function of folic acid.

Summary

It has been shown that the free phenylalanine and tyrosine levels in plasma of patients with acute leukemia are significantly higher than in normal patients. Tyrosine and tyrosine metabolites in the urine are apparently normal, and the hyperpigmentation that has been observed in patients receiving folic acid antagonists cannot be directly related to tyrosine excretion in the urine or to the elevated melanin precursors in the blood. Isoleucine values were higher in the plasma of leukemia patients than in normal individuals. Several leukemia patients showed unusually elevated valine and methionine values. Creatine and creatinine excretion were normal in patients with acute leukemia.

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SPANISH ABSTRACT

Metabolismo de los Aminoácidos en Enfermos con Leucemia Aguda

Los autores realizaron una serie de determinaciones de los aminoácidos libres del plasmo sanguíneo de sujetos normales y de enfermos con leucemia aguda al hacerse el diagnóstico y a intervalos durante su tratamiento con antifólicos y en el período de observación subsecuente. Igualmente llevaron a cabo determinaciones urinarias de los grupos fenólicos que representan los precursores y productos metabólicos de la tirosima y fenilalanina y dosificaciones de creatina y creatinina para evaluar la excreción de todas estas substancias.

Los resultados obtenidos consisten en una alza significativa de la fenilalanina y tirosina en los pacientes con leucemia en comparación con los individuos normales. La tirosina y sus metabolitos urinarios se encontraron aparentemente normales a pesar de los niveles mas altos de los aminoácidos sanguíneos.

La hiperpigmentación que ha sido observada en enfermos que reciben antagonistas del ácido fólico no puede relacionarse directamente con la excreción de la tirosina en la orina o con el aumento en la sangre de los precursores de la melanina, mas bien es probable que se deba a una interferencia por los antifólicos con los inhibidores normales de la melanogénesis en la piel blanca. Esta especulación requiere necesariamente pruebas adicionales. La isoleucina estaba mas alta en el plasma de pacientes de leucemia y los valores para la creatinina en la orina se encontraron dentro de los límites normales.

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OXALOSIS

Possible "Inborn Error of Metabolism" with Nephrolithiasis and Nephrocalcinosis Due to Calcium Oxalate as the Predominating Features

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RENAL calculi are not uncommon in children and diffuse calcification of the kidneys composed usually of mixtures of phosphate and carbonates have often been observed. However, disseminated deposits of calcium oxalate in the kidneys and other organs have been rarely recorded. Davis et al.[1] reported a case of extensive deposition of calcium oxalate crystals in the kidneys and bone marrow spaces in a 12 year old boy, and Carson[2] also reported a 4½ month old boy with diffuse deposition of calcium oxalate crystals in the kidneys.

The present authors had the opportunity to study a boy who had recurrent renal calculi from the age of 2 years and succumbed at the age of 7 years to renal failure. Autopsy revealed extensive deposits of calcium oxalate crystals in kidneys and bone marrow. Scattered crystals were also present in the heart, thymus, lungs, spleen and pituitary.

CASE REPORT

History and Physical Examination: D. L. was the only child of white parents of English extraction. Father stated that he passed one ureteral stone of unknown type in 1942.

Patient was well until age of 23 mo. when he developed recurrent painless hematuria. Two months later he passed a small yellow stone said to be about ⅛ in. in diameter. He was admitted to a local hospital, after 2 mo. Patient was of normal development and well nourished. Investigation revealed no abnormalities except for urinary system. Repeated urinalyses showed a faint trace of albumen, many red blood cells, a moderate number of pus cells and calcium oxalate crystals. Roentgenograms disclosed moderate bilateral hydronephrosis, a small radiopaque calculus in pelvis of R kidney and large stones in both ureters at uretero-pelvic junction. Calculi were removed from both sides at successive operations. These were light brown, spiculated, and on chemical examination were composed chiefly of calcium oxalate. He made an uneventful recovery after 42 days of hospitalization. Postoperative urinalyses were negative.

Patient is said to have remained symptomless and free from hematuria for 15 mo. although it is recorded that he passed more small stones 6 and 8 mo. after operation. He was readmitted to the hospital 15 mo. after operation and further investigation revealed a radiopaque stone at R uretero-pelvic junction and hydronephrosis on same side. Calculi were not located at operation. Repeated postoperative urinalyses showed oxalate crystals, red blood cells and pus cells. He was discharged with instruction to follow an alkali-producing diet low in oxalates and oxalic acid. He remained moderately well for 3 yr., when he had 3 episodes of ureteral colic within a week and passed a small stone. He was admitted to the Hospital for Sick Children after 3 mo. with a history of a transient L hemiparesis the morning of admission.

On physical examination patient was normally developed and well nourished. Routine physical examination was negative. A neurologic examination disclosed only somewhat hyperactive tendon

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reflexes and a slight unsteadiness of L hand on finger-to-nose test. There was no evidence of hemiparesis.

Results of various laboratory tests performed immediately revealed severe renal insufficiency and acidosis. These were as follows: blood pH 7.25; plasma CO_2 combining power 32.4 vol. %; serum Ca 8.3 mg./100 cc.; serum P 9.4 mg./100 cc. alkaline phosphatase 11.2 King-Armstrong u.; NPN 140 mg./100 cc. creatinine 9.3; serum Na 140 mEq./l.; K 7.75 mEq./l.; Cl 103.0 mEq./l.; serum protein 6.2 gm./100 cc.; albumen 3.0 gm./100 cc.; globulin 3.2 gm./100 cc.; Hgb. 12.6 gm./100 cc.; WBC count 4.9 thousand/cmm. (differential normal); tuberculin and Wassermann tests neg.; urinalysis: Sp. gr. 1.012, albumen and sugar neg.; Sulkowitch test neg.; cystine neg. (by paper chromatography) and microscopically an occasional pus cell.

Course: On the mornings of 3rd and 4th hospital days patient awakened with recurrence of L hemiparesis. Both attacks improved rapidly and there were no further similar episodes. However, his general condition showed progressive deterioration and by 14th hospital day NPN had risen to 222 mg./100 cc. On 17th hospital day an intestinal dialysis with 4.5% sodium sulphate administered through a duodenal tube was performed. This resulted in a slight temporary reduction in the NPN. On 20th hospital day, an oval rough brown calculus measuring 1 cm. in diameter was removed from L ureter. Chemical composition of this stone was calcium oxalate 60.0%, calcium carbonate 4.1%, organic debris 34.7% and unaccounted fraction 1.2%. It contained no cystine, uric acid or phosphate. Patient's condition steadily worsened. Terminally he developed a pericardial friction rub. He died on 39th hospital day at age of 6 yr., 11 mo., 5 yr. after first symptom of illness.

Autopsy: Gross examination.—Well-healed scars of previous abdominal operation were present. There was severe generalized oedema and bilateral pleural and peritoneal serous effusions.

Heart was not significantly enlarged but pericardial cavity was obliterated by a recent typical uremic fibrinous pericarditis.

Two parathyroids were identified. They were slightly enlarged, each measuring approximately 3 mm. in greatest diameter. Their combined weight was 46.7 mg.

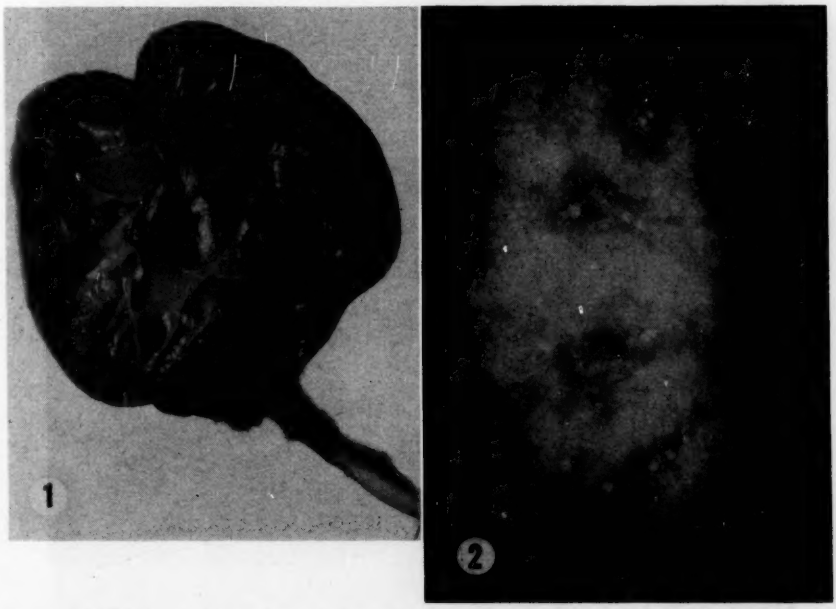
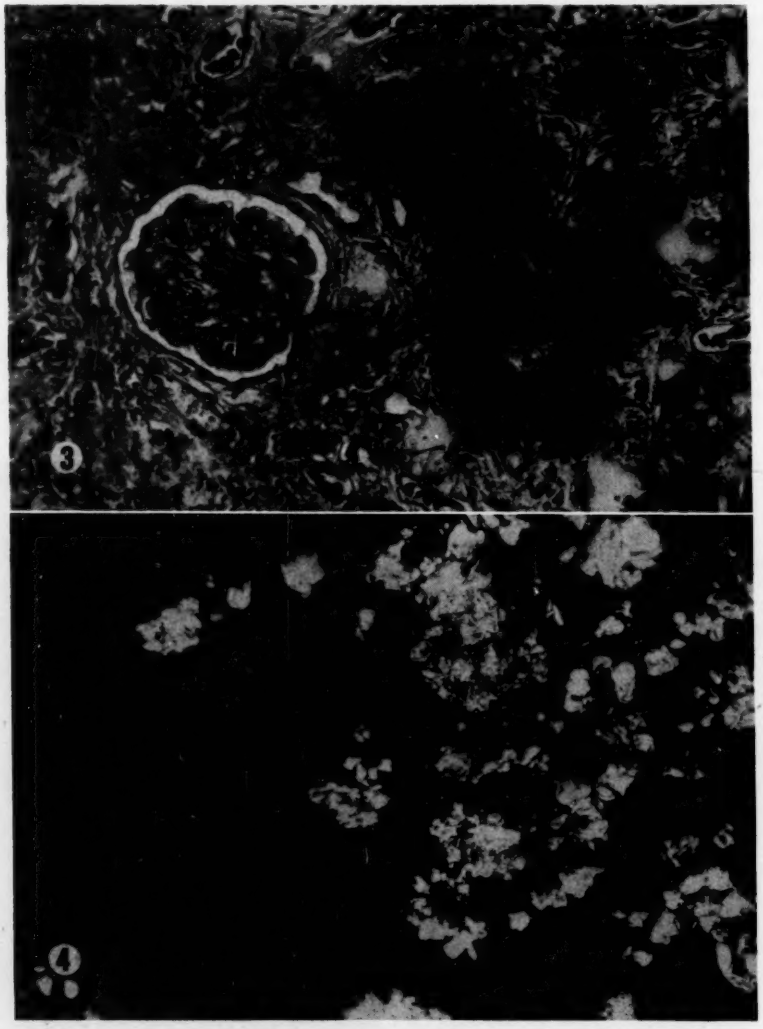


FIG. 1. Right kidney with moderate hydronephrosis. Large calcium oxalate calculus is present in lower pole. Sparkling crystalline deposits in parenchyma are not particularly well shown.
FIG. 2. RG of half of L kidney. There is diffuse increased opacity and numerous small opaque foci.

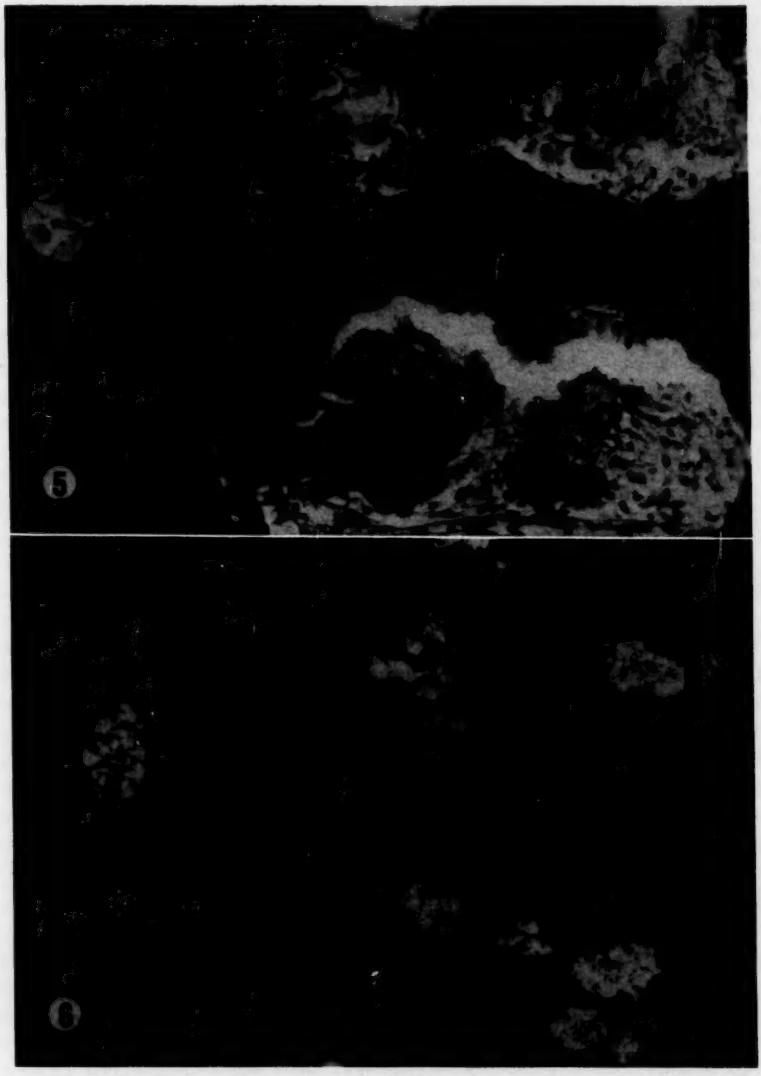
Grossly there were no bony abnormalities suggestive of renal rickets.

Both kidneys were of normal size (weights: right 77 gm., left 68 gm.). Capsules stripped easily. External surface was finely granular, pale yellow-brown and studded with innumerable yellowish pinpoint, shimmering, almost iridescent areas. Kidneys were firm and cut with a gritty sensation. There was a moderate bilateral hydronephrosis with thickening of walls of pelves and ureters but no significant dilatation of ureters (Fig. 1). In a major calyx of lower pole of R kidney, there was a yellowish brown, firm ovoid calculus with a finely granular surface measuring 1.7 cm. in greatest



FIGS. 3 and 4. Photomicrographs of same field in kidney cortex with ordinary light (3) and polarized light (4). Location and amount of calcium oxalate are well shown. Smudging in and about deposits is not due to poor technic but to staining of matrix associated with crystals. There is destruction of tubules and interstitial fibrosis. Relatively glomerulus shows only minimal involvement.

diameter. Pelvis of this kidney also contained a small amount of yellowish green pus which on culture yielded a Proteus species. Pelvis of L kidney was free of pus or calculi. Parenchyma of both kidneys was reduced in amount and usual markings of cortex and medulla were indistinct. Embedded in the yellow brown background of kidney substance were numerous tiny yellow sparkling crystalline-like bodies. Cut surface of kidney felt like fine sand-paper. RG of L kidney revealed diffusely increased opacity with many widely scattered small opaque shadows (Fig. 2). Urinary bladder and urethra were normal.



FIGS. 5 and 6. Photomicrographs of same field at costo-chondral junction of rib with ordinary light (5) and polarized light (6). Distribution of oxalate crystals is shown. Interesting feature is minimal reaction to deposits.

Microscopic examination.—The kidneys presented 5 interesting features: (1) diffuse intratubular deposition of calcium oxalate, (2) extensive tubular atrophy, affecting particularly the proximal convoluted tubules, (3) isolated foci of interstitial lymphocytic infiltration, (4) slight thickening of glomerular basement membranes, (5) condensation of renal parenchyma with slight interstitial fibrosis.

Calcium oxalate crystals were seen as irregular, very slightly yellowish semitransparent conglomerate crystalline masses predominantly within the lumina of convoluted tubules and occasionally in collecting tubules. These crystals were doubly refractile when examined with polarized light (Figs. 3 and 4). They did not take up routine stains but in and around each mass of crystals there was an irregular smudge of stain (pink in H & E) suggesting presence of a colloidal matrix. Tubules containing crystals as well as those which were free showed various degrees of degeneration. Epithelium of many proximal convoluted tubules had completely disappeared or remained as a flattened layer of cells. Thus, many crystals appeared to lie in the interstitial tissues. Collecting tubules were least affected. Except for those few containing masses of crystals, they appeared unaltered. In the cortex were irregular foci of lymphocytic infiltration. These had no definite relationship to deposits of crystals. The striking feature of glomeruli was their relatively normal appearance. Though an occasional degenerating or degenerated glomerular tuft was seen, majority of glomeruli remained unaffected apart from a slight thickening of the basement membranes. Bowman's capsules were not distended. Interstitial fibrosis was more apparent rather than real and the result of condensation of stroma occasioned by parenchymal degeneration. There was no foreign body reaction about the crystalline deposits.

In sections of bones from vertebra, sternum and ribs, there were numerous deposits of oxalate crystals. These were present in trabecular spaces and in the provisional zone of calcification (Figs. 5 and 6). They were apparently benign deposits as there was no evidence of reactive or rachitic changes.

In addition to the fibrinous pericarditis, heart showed an occasional rosette-like deposit of calcium oxalate crystals. Similar formations were present in thymus, lungs, spleen and pituitary. All these deposits were free of reactive changes.

Histologically parathyroids were normal. Brain showed no microscopic changes which would account for the transient hemiplegias.

Chemical analysis of kidney tissue.—Oxalate as oxalic acid was 6.56% of wet weight. Calcium was 3.18% of wet weight which was 0.26% in excess of that required to combine with all the oxalic acid. Calcium oxalate was 10.3% of wet weight or 36% of dry weight.

Discussion

The incidence of urinary calculi in children varies in different parts of the world. Campbell[3] found 67 cases in 15,010 autopsies, an incidence of 0.42% in the United States. H. P. W. White[4] stated that calculi were less common in the upper urinary tract in children and noted that the majority of calculi caused symptoms between the ages of 3 and 6 years, although they might be present at any age. There is a marked preponderance of incidence in the male. He also noted that the majority of 160 vesical calculi from children under 15 years of age in the Museum of the Royal College of Surgeons in London, England, was composed chiefly of calcium oxalate or ammonium urate and that these occurred with about equal frequency. Campbell has stated that the incidence of oxalate calculi in children ranks next to those composed of uric acid and urates.

Calcium oxalate stones are the most radiopaque of all calculi and hence frequently show up as an incidental or unexpected finding in roentgenograms of the abdomen which have been taken for other purposes. There is apparently a geographic variation in the incidence of oxalate stones. In Central Europe, in the so-called "stone belt," during the two decades following the first World War, there was a considerable increase in the incidence of urinary calculi. Grossmann[5] has estimated that over 65% of these were oxalate calculi and noted that in these cases there were no significant changes in the

chemical composition of the urine to account for these findings. Although a large number of reports have appeared in respect to oxalate calculi incriminating such factors as high dietary intake of oxalates and oxalic acid, poor nutrition, vitamin deficiency, and magnesium deficiency in the development of these stones, Jeghers and Murphy[6] in their review on oxalate metabolism came to the conclusion that the cause of these calculi was obscure. In the patient reported here at no time was there any evidence that the diet was unusual. Sex may possibly be a factor as the two previously reported patients[1, 2] and this patient were males.

Parenchymal nephrocalcinosis of varying degree of severity may be encountered in a wide variety of conditions.[7] Minor degrees which cannot be recognized histologically or demonstrated by histochemical methods may be determined by a chemical analysis of the tissue. When the presence of calcium is revealed by histologic or histochemical means it is present in relatively high concentrations and usually in an amorphous state. It reacts positively to Von Kossa stain and is present presumably in the form of phosphates and/or carbonates. The case reported here was unusual in that the calcium was in the form of crystalline oxalates and did not give a positive Von Kossa reaction.

It is unlikely that this particular type of calcinosis represents a defect in calcium metabolism. It would seem rather to be the result of an inborn error of metabolism in which oxalic acid is formed in excessive amounts and combines with calcium to form a relatively inert compound. The fact that the patient was on a diet low in oxalates and oxalic acid for some years prior to death would seem to preclude the possibility of an abnormally high intake in this particular incidence. Although it is generally considered that most of the oxalates excreted are of exogenous origin there is good evidence to indicate that there is some endogenous formation.[6] There is a possibility that even though the rate of absorption or production of oxalates is within normal limits an abnormality of the colloidal milieu of the body could result in a precipitation of calcium oxalates in the tissues.

Chemically very little is known about oxalic acid metabolism. It has been suggested that oxalic acid may be formed as an abnormal break-down product of the amino acid glycine.[8] However, the "two carbon" moiety or fragment is so ubiquitous in the metabolism of the body that under abnormal conditions oxalic acid could conceivably appear as the end product of wide variety of biochemical systems.

Calcium oxalate in the tissues appears to be a singularly inert substance. Tissue reaction was minimal. The renal insufficiency was in major part due to actual replacement of renal parenchyma and plugging of the tubules by conglomerate masses of crystals. An additional factor was a moderate degree of bilateral hydronephrosis resulting from the recurrent calculi.

Summary

A case is reported of renal failure in a boy subsequent to recurrent calcium oxalate urinary calculi. The post mortem disclosed widespread deposits in the tissues of calcium oxalate crystals. These were particularly prominent in the kidneys and bone marrow.

It is suggested that this is the end result of an "inborn error of metabolism" in which there was an excessive formation of oxalic acid.

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SPANISH ABSTRACT

Oxalosis

Un Posible "Error Innato del Metabolismo," con Nefrolitiasis y Nefrocalcinosis como Características Predominantes debidas al Oxalato de Calcio

La historia clínica relata el caso de un niño cuyo padre arrojó un cálculo urinario. El cuadro del enfermo se inicia a los 24 meses con hematuria recurrente no dolorosa; dos meses después arroja un cálculo pequeño de color amarillo. Estaba bien desarrollado y nutrido. Los exámenes de orina demostraron huellas de albúmina, eritrocitos, piocitos y cristales de oxalato de calcio y radiológicamente se encontró hidronefrosis bilateral moderada, un cálculo en la pelvis renal derecha y otro en cada uno de los ureteros al nivel del estrechamiento pélvico. Fueron extirpados quirúrgicamente y se demostró que eran de oxalato de calcio. Permaneció asintomático por unos 14 meses, aunque en ese intervalo arrojó algunos cálculos pequeños. Un nuevo estudio de rayos X demostró otro cálculo en el uretero derecho e hidronefrosis del mismo lado, pero en la operación no pudo localizarse y continuó con orina con piocitos, eritrocitos y cristales. Se le recomendó dieta pobre en oxalatos y ácido oxálico. Estuvo mas o menos bien por 3 años cuando tuvo tres episodios de cólicos ureterales durante una semana y expulsó otro cálculo pequeño y en enero del año actual se internó con historia de una hemiparesis izquierda transitoria, pero el exámen neurológico solo dió hiperreflexia tendinosa ligera e incordinación ligera también de la mano izquierda. La química sanguínea reveló insuficiencia renal severa y acidosis. En el tercero y cuarto días de admitido amaneció con hemiparesia izquierda que mejoró rápidamente pero su insuficiencia renal se acentuó; apareció brote pericárdico y murió a los 6 años 11 meses, a los 5 años de iniciarse su enfermedad, después de operarse por última vez para hacer la extirpación de otro cálculo del uretero izquierdo que químicamente estaba integrado en un 60% de oxalato de calcio y 4.1% de carbonato de calcio.

A la autopsia se encontró macroscópicamente anasarca severa, pericarditis fibrinosa urémica reciente, riñones de tamaño normal, aspecto externo finamente granuloso, café amarillento pálido, y sembrados de innumerable puntilleo amarillento, luminoso, casi iridescente. Los riñones eran de consistencia firme con una sensación arenosa. Había hidronefrosis bilateral moderada y un cálculo en el cáliz mayor e inferior del riñón derecho. El parénquima estaba reducido en cantidad y embebido en él habían numerosos cuerpos diminutos de color amarillo que brillaban como cristales. La superficie al corte se sentía como lija. Microscópicamente presentaban cinco características interesantes: concreción intratubular difusa de oxalatos de calcio, atrofia tubular extensa principalmente proximal, focos aislados de infiltrado linfocítico intersticial, engrosamiento de la membrana basal glomerular y condensación del parénquima renal con fibrosis intersticial ligera. En las vértebras, esternón y costillas había numerosos depósitos de cristales.

El corazón, timo, pulmones, bazo y pituitaria presentaban ocasionalmente depósitos de cristales de oxalato de calcio que adoptaban la forma de rosetas.

Las paratiroides estaban normales y el cerebro también. Químicamente el oxalato de calcio representaba el 36% del peso del tejido renal desecado.

Es improbable que este tipo de calcinosis represente un defecto del metabolismo del calcio sino mas bien el resultado de un error innato del metabolismo en el cual el ácido oxálico se forma en cantidades excesivas y se combina con el calcio para formar un compuesto relativamente inerte, aunque también es posible que aún siendo normal la absorción o producción de oxalatos exista una anormalidad del medio coloidal del organismo que provoque la precipitación de los oxalatos de calcio en los tejidos.

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USE OF I^{131}-LABELED PROTEIN IN THE STUDY OF PROTEIN DIGESTION AND ABSORPTION IN CHILDREN WITH AND WITHOUT CYSTIC FIBROSIS OF THE PANCREAS

By PAUL S. LAVIK, PH.D., LEROY W. MATTHEWS, M.D., G. W. BUCKALOO, M.S., FRANCES J. LEMM, SAMUEL SPECTOR, M.D., AND HYMER L. FRIEDELL, M.D.
Cleveland

DURING the past two decades several studies of protein digestion and absorption have been carried out both in normal individuals and in patients with various diseases. A diminished retention of dietary protein in cystic fibrosis of the pancreas was demonstrated by Shohl, May and Shwachman[1] with balance studies and by Andersen[2] with stool analyses. The methods employed by these investigators were accurate but too laborious for use as routine diagnostic procedures. West, Wilson and Eyles[3] studied the blood amino-nitrogen levels after the ingestion of a protein meal and found a significantly lower rise in blood amino acids in the children with cystic fibrosis of the pancreas. Though widely used as a diagnostic aid, this method is subject to various sources of error, and it lacks both specificity and sensitivity. It is the purpose of this paper to describe a simple and accurate method which determines the efficiency of protein digestion and absorption by measuring the isotope content of the feces after the oral ingestion of I^{131}-labeled protein.

METHODS AND MATERIALS

In preparing I^{131}-labeled protein employed in this study, calcium caseinate* was extracted with alcohol and ether to remove lipids and then iodinated† by a procedure similar to that described by Fine and Seligman.[4] This results in a product which contains sufficient I^{131} for tracer purposes but not enough to alter significantly the biochemical properties of the protein (Warren and Dixon[5]). There was no detectable deterioration of the I^{131}-labeled protein when stored in refrigerator for 1 to 2 wk., but as a precautionary step all preparations over 2 wk. of age were re-dialyzed before use.

Test meal was prepared immediately before use by suspending the following ingredients in 100 to 200 cc. of water in a Waring blendor operating at reduced speed: I^{131}-labeled calcium caseinate (usually 1.0 μc./kg. body weight), nonradioactive calcium caseinate (1.75 gm./kg. body weight) and any other components as desired (e.g., glucose, flavoring).

To determine isotope content of fecal samples, each collecting jar with its fecal specimen was placed in a fixed position next to a scintillation counter (MacIntyre[6]) as shown in Fig. 1 and the γ rays from the I^{131} counted. By comparison with a standard solution containing a known amount of I^{131} in a volume equal to that of fecal sample, it was possible to calculate the total μc./specimen. Special preparation of fecal samples for this method of counting was unnecessary except to insure a uniform distribution of the isotope; this was readily done with a motor driven stirrer or with an Oster mixer. In measuring isotope content of blood and urine samples, 3 methods were used.

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(Received for publication July 22, 1952.)

* Casec, available from Mead Johnson & Company.

† I^{131} obtained from the Isotopes Division of the U. S. Atomic Energy Commission.

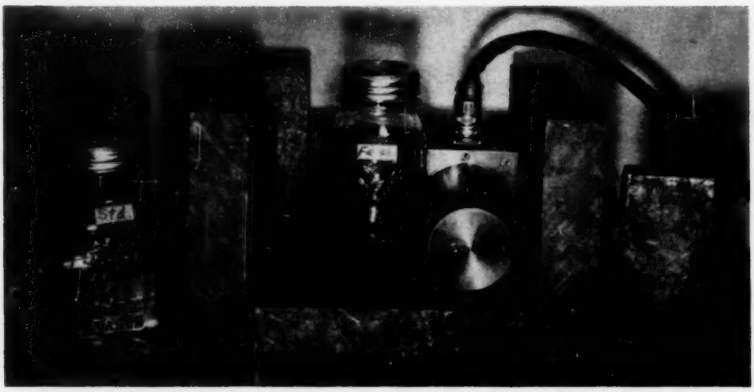

FIG. 1. Scintillation counter used for measuring I^{131} content of fecal and urine samples.

Where maximum sensitivity was required, samples were dried and assayed under an end-window counter; however, most urine samples and some blood samples were conveniently assayed directly in a liquid counter (Lavik et al.[7]) or in a scintillation counter.

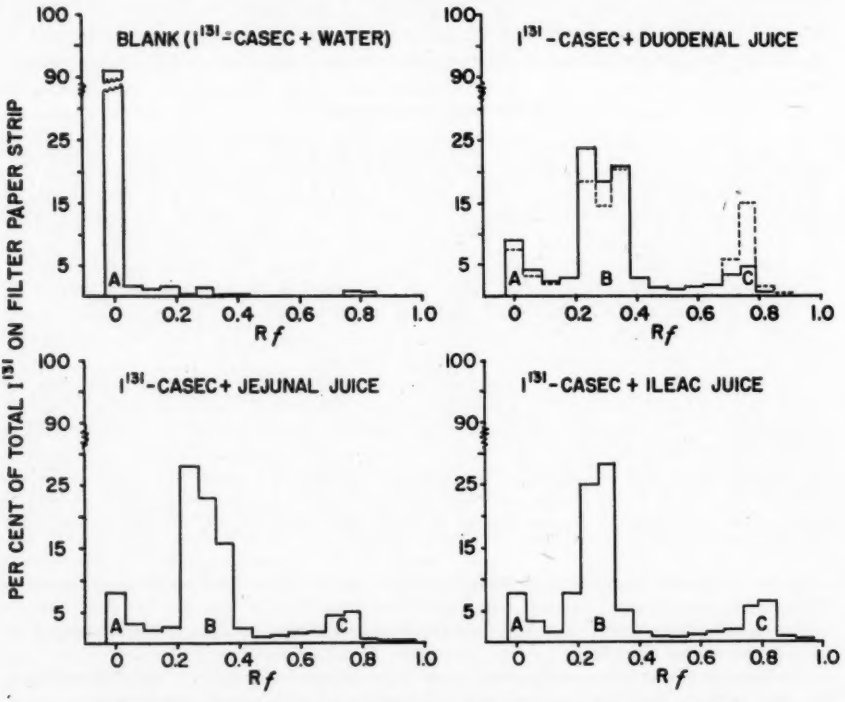

CHART 1. Chromatographic separation of radioactive products formed in incubation mixtures of I^{131}-labeled Casec and digestive juices of dog. Broken-line chromatogram = incubation mixture containing duodenal juice, I^{131}-labeled Casec, and added iodide I^{131}.

Experimental

To test the feasibility of using I^{131}-labeled protein in studying protein digestion and absorption, some preliminary experiments were carried out in dogs. It was first necessary to establish whether the isotope remains bound to the iodinated tyrosine of the protein molecule during the process of digestion, i.e., whether the radioactivity accurately reflects the movement of I^{131}-labeled tyrosine originally present in the fed protein. Fasted dogs were fed a test meal of nonradioactive calcium caseinate to stimulate the flow of digestive juice, and 2 to 3 hours later the animals were killed. The gastrointestinal tracts were removed and divided into the gastric, duodenal, jejunal, iliac, and colonic segments. The content of each segment was rinsed into a breaker with a minimum of water. A known amount of I^{131}-labeled calcium caseinate was mixed with an aliquot of the digestive fluid from each segment and incubated at 37°C. for about two hours. The distribution of isotope among the various iodinated compounds was then determined for each incubation mixture by the filter paper-chromatographic technic described by Taurog et al.,[8, 9] using the collidine-water mixture as the developing solvent. Although adequate digestion oc-

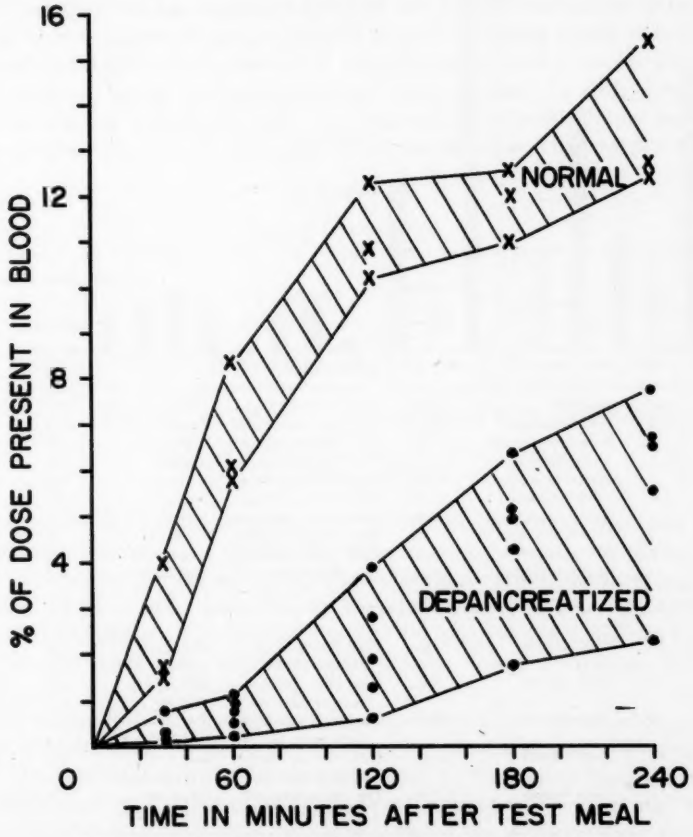

Chart 2. Uptake of I^{131} in blood of normal and depancreatized dogs after test meal of I^{131}-labeled protein.

curred in all cases, only the digestive fluids from the small intestine liberated a significant amount of inorganic I^{131}. Chart 1 shows the amount of radioactivity (in per cent of the total) found at various positions along each filter paper strip. Based on the behavior of known compounds in this system,[9] peak A represents unhydrolyzed I^{131}-labeled protein; peak B, mainly monoiodotyrosine with some diiodotyrosine; and peak C, inorganic iodide. The isotope found between the main peaks was not inorganic iodide formed during the incubation period, because when radioactive iodide was added to an aliquot of the duodenal incubation mixture, the chromatogram prepared in the same manner showed enhanced radioactivity only at peak C (Rf, 0.7-0.8). This is shown graphically in chart 1 by the broken line diagram. It is evident that, during a two hour incubation with digestive juices from the small intestine, most of the isotope remained attached either to the protein (A) or to the tyrosine moieties (B), and 12% or less was present as inorganic iodide (C). These results suggest that if the I^{131}-labeled protein were administered orally, the isotope could be used to trace the protein and any iodinated tyrosine liberated by digestion in the gastrointestinal tract.

The possible use of I^{131}-labeled protein in studying protein digestion and absorption was further demonstrated (Lavik and Miller[10]) in normal and depancreatized dogs fed a test meal of labeled protein. The blood absorption curves determined 3 to 17 days post-operatively showed a much slower rise than was observed in the same dogs before pancreatectomy (chart 2). Although other explanations could be offered, the slower entry of the isotope into the blood of the depancreatized dogs was probably due to a deficiency of digestive enzymes and hence a diminished liberation of amino acids (I^{131}-labeled tyrosine).

TABLE 1

EXPERIMENTAL SUBJECTS

Patients	Age (yr.)	Diagnosis	Duration of Disease	Condition of Patient	Gastrointestinal Function		
					Character of Stools	Stools/Day	Tryptic Activity*
"Control" Patients							
J.He.	6.5	Leukemia	3 wk.	Fair. Good nutritional	Normal	1	Positive
K.B.	5	Lymphosarcoma	6 wk.	Fair. Good nutritional	Normal	1–2	Positive
F.I.	9	Bronchopneumonia	3 days	Good. Good nutritional	Normal	1	Positive
D.G.	5	Bronchiectasis	4.5 yr.	Poor. Poor nutritional	Normal	1–2	Positive†
K.K.	2	Mental retardation	2 yr.	Fair. Good nutritional	Normal	1–2	Positive
J.J.	6	Chronic asthma	5 yr.	Good. Fair nutritional	Normal	1	Positive
L.W.	6	RML pneumonia	4 days	Good. Good nutritional	Normal	1	Positive
M.S.	7	Coarctation of aorta	7 yr.	Good. Good nutritional	Normal	1	Positive
W.B.	8	Mental retardation	8 yr.	Good. Good nutritional	Constipated	0–1	Positive
A.W.	3.5	Spastic paraplegia	3 yr.	Poor. Malnutrition	Constipated	0–1	Positive
Patients with Cystic Fibrosis of Pancreas							
G.D.	2.5	Cystic fibrosis	18 mo.	Poor. Malnutrition; Marked pulm. dis.	Bulky, soft brown	2–4	Negative
P.K.	3.5	Cystic fibrosis	3 yr.	Poor. Malnutrition; Marked pulm. dis.	Bulky, soft brown	2–4	Negative
J.Ho.	1.6	Cystic fibrosis	18 mo.	Fair. Good nutritional; Early pulm. dis.	Soft, yellow brown	1–3	Negative
T.M.	4.5	Cystic fibrosis	4 yr.	Poor. Poor nutritional; Marked pulm. dis.	Bulky, soft, foamy, brown	2–4	Negative
M.J.	4	Cystic fibrosis	3.5 yr.	Fair. Fair nutritional; Minimal pulm. dis.	Soft, foamy, bulky, brown	3–4	Negative

* "Positive" represents tryptic activity in stool at dilutions of 1:80 or greater; "Negative" represents absence of tryptic activity at dilutions greater than 1:10.

† Negative at dilutions greater than 1:40.

Application of the Method to Studies of Protein Digestion and Absorption in Children: Ten patients with diseases which did not specifically involve the gastrointestinal tract and five patients with cystic fibrosis of the pancreas were studied. Pertinent data on the subjects are presented in table 1. Each patient received 4 to 10 drops of Lugol's solution every 12 hours during the 24 hours preceding and for four days after the test meal to block the thyroid uptake of I^{131}. The patients were fasted for 12 hours and the test meal described was then administered orally in place of breakfast; the patients received the

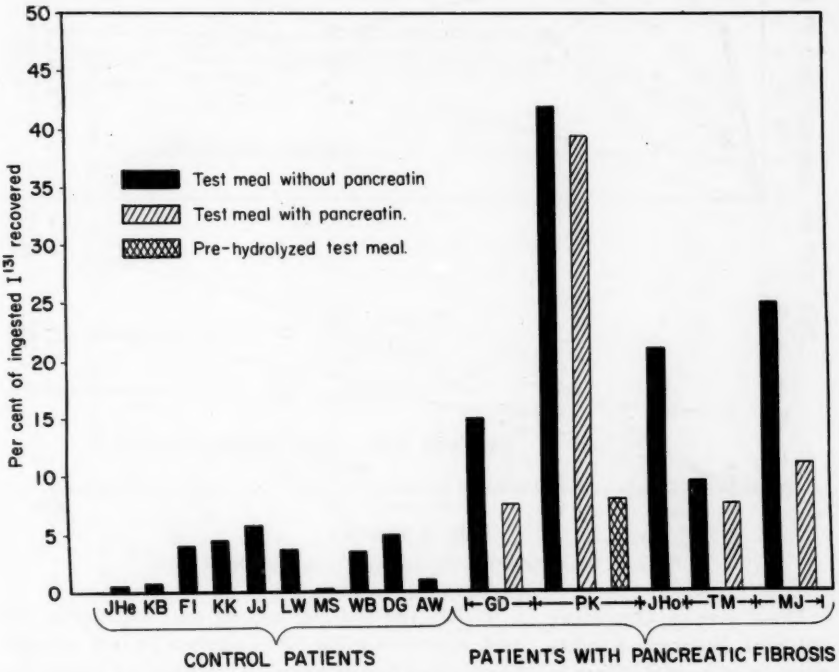

CHART 3. Recovery of I^{131} in feces during 1st 72 hr. following test meal of I^{131}-labeled Casec.

usual hospital diet for all subsequent meals. In each of the five patients with cystic fibrosis of the pancreas, pancreatin was withheld for three days prior to and during the initial test. In four of these patients the test was subsequently repeated with the simultaneous administration of pancreatin U.S.P. 1.0 gm. The administration of 1 μc. of labeled protein/kg. body weight was found to be adequate for assay purposes and this dosage is well within the safety limits approved by the Atomic Energy Commission for use in humans.

For three days after the test meal, stool specimens were collected and stored in pint or quart jars containing 0.1 N NaOH 100 cc.; care was taken to keep the feces completely free of urine. The urine was also quantitatively collected over the same three day period in bottles containing 5 to 6 pellets of NaOH. In infants a metabolism bed was used to obtain successive six hour urine specimens, whereas each voided specimen was collected separately in the case of older cooperative patients. The isotope contents of the fecal and urine samples are expressed as per cent of the ingested I^{131}.

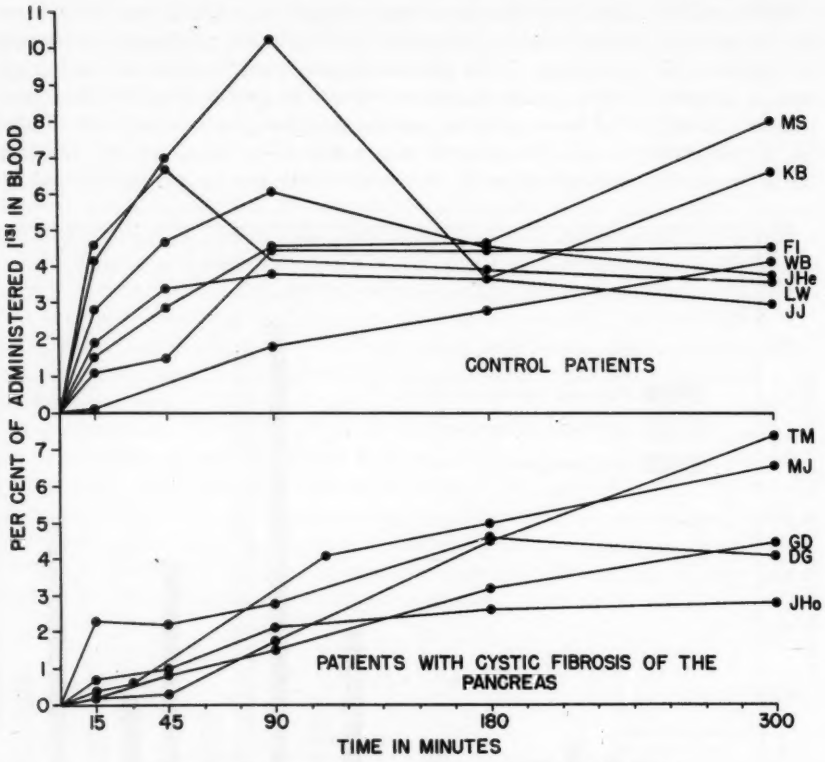

CHART 4. Blood level of I^{131} following test meal of labeled Casec.

Blood samples were drawn 15, 45, 90, 180 and 300 minutes after ingestion of the test meal. Heparinized venous blood, as well as whole blood obtained by heel or finger puncture, were used. When heparinized blood was employed, the plasma was assayed and the number of counts/cc. whole blood calculated on the basis of the hematocrit reading. Results were expressed as per cent of ingested I^{131} present in the total blood volume (assumed to be 10% of body weight).

RESULTS

The most striking difference between the results obtained in the children with relatively normal gastrointestinal function and those with cystic fibrosis of the pancreas was found in the amount of I^{131} excreted in the feces. Among the "controls" (table 1), the fecal excretion did not exceed 6% of the isotope consumed in the form of labeled protein (chart 3). In addition to the "controls," one child with celiac syndrome was tested and had a fecal excretion of 5%. In the children with pancreatic fibrosis, not receiving pancreatin, the fecal excretion ranged from 10% to 40%, and averaged 22.5% When the test meal was administered with pancreatin, the fecal excretion of the isotope was decreased about 50% in two cases but was reduced very little in the other two. The test was repeated in one of the latter two patients (P.K.) using a test meal which was hydrolyzed with pancreatin before administration. Fecal excretion of I^{131} in this case amounted to only 8% of the ingested dose, in contrast to the 40% excretion found after the normal test meal.

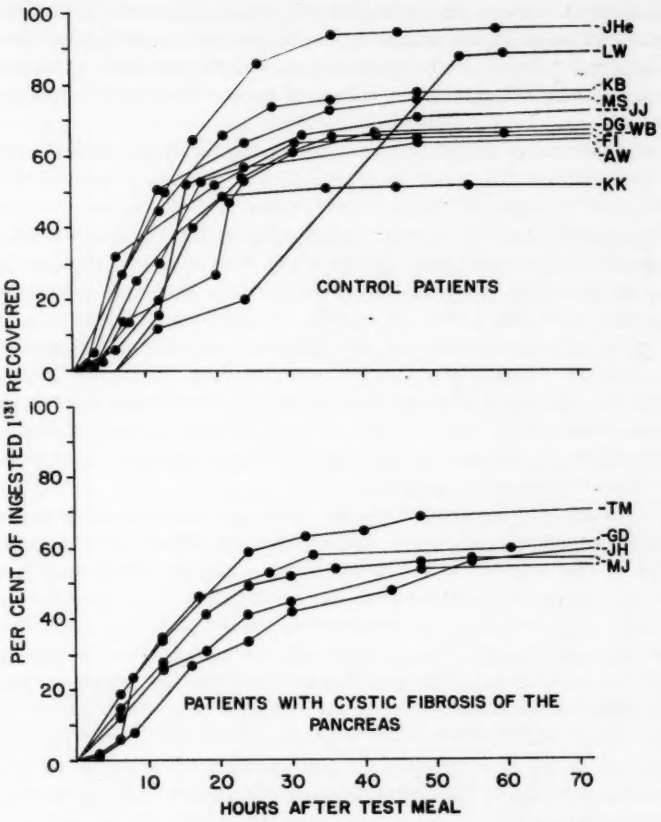

CHART 5. Recovery of I^{131} in urine after test meal of labeled Casec.

The amount of I^{131} present in the blood at intervals after the ingestion of the test meal by each patient is shown in chart 4. Children with pancreatic fibrosis showed a slower rise in blood radioactivity than did the controls, but the difference was not striking. The children with pancreatic fibrosis also showed a slower rate and a lower total excretion of isotope in the urine (chart 5), but the differences between the two groups were not sufficient to be of real diagnostic value. The total recovery of I^{131} in the urine averaged 74% in the control patients and 54% in the patients with cystic fibrosis of the pancreas.

DISCUSSION

In studies of digestive disorders it is often desirable to determine what proportion of ingested protein is actually absorbed under varying conditions of diet and therapy. It is impossible to follow the movement of ingested proteins or their hydrolytic products in the gastrointestinal tract unless they are appropriately labeled. That I^{131} could be used for this purpose was suggested by the authors' *in vitro* studies with dog digestive juices which indicated that 88% or more of the I^{131} remains attached to the tyrosine of the iodinated protein molecule during the process of digestion. Accordingly, if a test meal containing a known amount of I^{131}-labeled protein is administered orally and the amount

of isotope excreted in the feces is measured, the amount of protein absorbed can be estimated. One application of this procedure was demonstrated in the present study. When children with cystic fibrosis of the pancreas were fed the test meal, 15 to 43% of the isotope was excreted in feces, whereas in none of the control patients did the fecal excretion exceed 6%.

By repeating the test in the patients with cystic fibrosis of the pancreas, the effectiveness of pancreatin administration could be evaluated. The quantity of pancreatin employed reduced the fecal excretion of isotope in two patients to about one-half that observed in the absence of pancreatin. The relatively minor effect of pancreatin in Patients P.K. and T.M. suggested that either the dose was not adequate or that these children might have a defect in the absorption of amino acids rather than the digestion of proteins. The latter did not appear to be true in the case of P.K., for when the test meal was hydrolyzed with pancreatin prior to administration, only 8% of the ingested isotope appeared in the feces. Since the latter value is only slightly above those found in the control patients, it is evident that this child lacked the ability to digest protein effectively, and this accounted for the poor absorption of ingested protein. Since the data indicated that pancreatin is not equally effective in all patients, one application of this method would be to evaluate the effectiveness of pancreatin administration.

The observation by Albert and Keating[11] that iodinated compounds pass from the blood into the gastrointestinal tract in humans does not detract from the usefulness of the method. If this occurred in the authors' control patients, which is probable, most of the isotope entering the gastrointestinal tract in this manner was evidently reabsorbed, since the total fecal excretion of isotope amounted to less than 6% of the ingested I^{131}. Because of the bulky stools in the children with cystic fibrosis of the pancreas, interference with the reabsorption of this I^{131} from the intestine could explain the greater fecal loss of the administered isotope. However, this was apparently not an important factor in Patient P.K. whose fecal excretion of I^{131} fell from 40% to 8% when prehydrolyzed protein was used in the test meal instead of the usual calcium caseinate. The decrease occurred despite the poor digestion of subsequent meals and the passing of bulky stools during the balance of the study.

The evaluation of protein digestion and absorption by measuring the fecal excretion of isotope after feeding a test meal of I^{131}-labeled protein has a number of advantages over other methods. By comparison, the nitrogen balance method is laborious and time-consuming. The determination of unabsorbed protein and amino acids in the feces also appears to be a more sensitive measure of protein digestion and absorption than does the determination of changes in blood amino-nitrogen after the ingestion of a protein test meal. The blood absorption curves obtained in the authors' studies with I^{131}-labeled protein did not show a clear-cut difference between the control children and those with cystic fibrosis of the pancreas, i.e., some of the curves in the two groups were found to overlap. Similar results were obtained when the blood amino-nitrogen levels following a protein test meal were studied by the method of West et al.[3] In contrast, when a comparison was made of the amount of isotope excreted in the feces after a test meal of labeled protein, no overlap was observed. One explanation for this difference is that the results obtained by fecal analyses over a period of 1 to 3 days are not influenced significantly by variations in gastric emptying time, by slight changes in intestinal motility, and by other factors which can affect profoundly the rate of digestion and absorption.

The determination of total urinary excretion of the isotope for three days after the

test meal of I^{131}-labeled protein did not provide a reliable measure of the absorbed protein. As observed by Kelsey et al.[12] and others, an appreciable amount (10 to 40%) of the administered isotope was not recovered in either urine or feces during the period of study. This variability in the amount of isotope retained in the tissues would have a direct effect on the urinary excretion values and probably accounts for the overlapping urinary excretion curves in the two groups of children.

Summary

A method is described for evaluating protein digestion and absorption by measuring the fecal excretion of isotope after the administration of a test meal of I^{131}-labeled protein. Application of this method to 10 children without gastrointestinal disease and to five with cystic fibrosis of the pancreas revealed the following:

1. Less than 6% of the ingested isotope was excreted in the feces of the "control" subjects.

2. A 10 to 40% (av. 22.5%) fecal excretion of the ingested isotope occurred in the children with cystic fibrosis of the pancreas.

3. A 50% decrease in the fecal excretion of isotope resulted in 2 of 4 children with cystic fibrosis of the pancreas when pancreatin was fed with the test meal.

4. One patient with cystic fibrosis of the pancreas, who after receiving pancreatin still excreted 40% or more of the ingested isotope in the feces, excreted only 8% when the test was repeated with prehydrolyzed protein.

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SPANISH ABSTRACT

Uso de la Proteína Unida al I^{131} en el Estudio de la Digestión y Absorción Protéica en Niños con y sin Fibrosis Quística del Páncreas

Los autores describen un método para estudiar la digestión y absorción protéica que tiene ventajas sobre, los de balance y análisis de las evacuaciones que se han usado en enfermos con fibrosis quística del pancreas por ser muy laboriosos y también sobre la determinación de los niveles sanguíneos de aminoácidos después de la ingestión de un alimento protéico, por su falta de especificidad, sensibilidad y por estar sujeto a varias causas de error.

Usan la proteina con yodo irradiado (I^{131}) preparándola con caseinato de calcio al cual le eliminan los lípidos y en seguida la yodinan obteniéndose así un producto que contiene suficiente cantidad de I^{131} unido a la proteína para ser usado como indicador, pero sin alterar en forma significativa sus propiedades bioquímicas. El alimento de la prueba fué preparado inmediatamente antes de usarlo mezclando el caseinato de calcio I^{131} a razón de 1 microgramo por Kg. de peso con 1.75 gramos por Kg. de peso de caseinato de calcio no-radioactivo, en unos 100-200 c.c. de agua. La determinación del contenido de isótopo en las muestras fecales se hizo por medio de un contador de cintilaciones contando los rayos gamma del I^{131}. Comparando con una solución standard conteniendo una cantidad conocida de I^{131} en un volumen igual al de la muestra fecal fué posible calcular el total de microgramos en cada especímen. Igualmente se midió el contenido de isótopo en las muestras de sangre y orina por medio de un contador de líquido o de cintilación aunque si se requería un máximo de sensibilidad las muestras de sangre u orina se desecaban y se usaba un contador de ventana.

Antes de realizar sus experimentos en los niños los autores tuvieron que determinar si el isótopo permanecía unido a la tirosina yodinada de la molécula protéica durante el proceso de digestión, es decir, si la radioctividad refleja exactamente el movimiento del I^{131} unido a la tirosina originalmente presente en la proteína administrada. Esto fué demostrado satisfactoriamente en experimentos en perros.

Se estudiaron a continuación 10 niños enfermos de padecimientos que no afectaban específicamente su aparato digestivo y 5 con fibrosis quística. Cada uno recibió un poco de solución de sangre durante las 24 horas previas a la prueba para bloquear la toma de I^{131} por parte de la tiroides y después de 12 horas de ayuno se les administró como almuerzo el alimento de prueba. A los enfermos de fibrosis pancreática se les suspendió la pancreatina 3 días antes y durante la prueba inicial repitiéndose esta en 4 de ellos con la administración simultánea de pancreatina. La administración de 1 microgramo de proteína con yodo radioactivo fué adecuada y esta dosis está dentro de los límites de seguridad para su uso en seres humanos establecidos por la Comisión de Energía Atómica.

En los 3 días siguientes al alimento de prueba se recogieron todas las evacuaciones y todas las orinas usando cuando fué necesario camas de metabolismo; igualmente se tomaron muestras de sangre a los 15, 45, 90, 180 y 300 minutos después del alimento de prueba. Los resultados fueron expresados en % del I^{131} ingerido tanto para las heces como las orinas y la sangre, pero haciendo el cálculo en esta última de acuerdo con lo que tendría de isótopo el volumen sanguíneo total asumiento que este correspondía al 10% del peso.

Los resultados demostraron una diferencia notable entre la cantidad de I^{131} excretada en las heces de ambos grupos pues mientras en el grupo control no excedió del 6% del total de isótopo ingerido, en los enfermos de fibrosis quística varió del 10 al 40% lo cual demuestra obviamente una falta de absorción proteíca, y que ésta fué debida a déficit en la digestión protéica se comprobó en 2 de los enfermos de los 4 en quiénes subsecuentemente se le repitió la prueba con administración de pancreatina pues la excreción fecal del isótopo se redujo a la mitad de la que presentaron sin ella. El efecto relativamente menor de la pancreatina en los otros 2 enfermos sugiere que la dosis fué inadecuada o que estos enfermos tenían un defecto en absorción de los aminoácidos mas bien que en la digestión de las proteínas. Sin embargo, en uno de ellos se repitió la prueba con el alimento previamente hidrolisado con pancreatina y la excreción se redujo del 40 al 8% lo cual muestra claramente que tenía efectivamente falta de digestión protéica y esa era la causa de la escasa absorción protéica.

Como los autores encontraron en sus experimentos con jugos digestivos del perro que el 88% o mas del I^{131} permanece unido a la tirosina de la molécula protéica yodada, durante el proceso de su digestión, si se dá un alimento de prueba con una cantidad conocida de proteína etiquetada o marcada con I^{131} y se mide la cantidad de isótopo excretada en las evacuaciones, se puede estimar la cantidad de proteína absorvida.

Además, por medio de este método, se puede evaluar la efectividad de la administración de pancreatina en los enfermos de fibrosis pancreática, que bien sabido es variable en ellos.

Western Reserve University

FERROUS SULFATE POISONING

Report of a Fatal Case

By LIEUT. LEROY K. BRANCH, M.C., U.S.N.R.
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FERROUS sulfate has been considered a nontoxic drug, regardless of the amount ingested. Medicinal iron is not mentioned as a possible cause of fatal poisoning in textbooks of pediatrics or pharmacology.

The purpose of this paper is to report a case of ferrous sulfate poisoning with fatal outcome in a 29 month old child.

REVIEW OF THE LITERATURE

Only a few cases of iron toxicity were reported before 1947. These were reviewed by Smith, Jones and Cochran[1] in 1950.

Veeder[2] reviewed 8 fatal and 8 nonfatal cases of poisoning from accidental ingestion of medicinal iron reported since 1947. Smith's editorial[3] pointed out the importance of knowing the potential toxicity of ferrous sulfate and other medicaments containing iron.

Forbes[4] initiated current interest in this problem by reporting two fatal cases of ferrous sulfate poisoning in 1947. Later by experimentation he established the lethal dose of ferrous sulfate in cats as 0.065 gm./64 gm. body weight. Thompson[5, 6] reported two fatal human cases in 1947. He recorded four other cases in 1950, one of which was fatal. Foucar et al.[7] reported a 26 year old man who died three hours after ingestion of one-fourth pound of ferrous sulfate. Roxburgh[8] made no claim for the value of 2,3 dimercaptopropanol (BAL) used in the treatment of a 16 month old patient who recovered from iron poisoning. Lindquist[9] reported a nonfatal case of ingestion of ferric chloride tablets and mentioned a nonfatal case of Magnussen's which had not been reported. Smith, Jones and Cochran[1] described a case in a 17 month old child with autopsy findings.

Murphy and his associates[10] recorded the recovery of a 30 month old child after ingestion of 15 gm. ferrous sulfate (1.28 gm./kg. body weight). Spencer[11] described eight cases of iron poisoning in the British literature. Four of these were fatal. The number of reported cases of iron poisoning in children totals 25 since 1947 with the recent description of one fatal and two nonfatal cases by Duffy and Diehl[12] and a fatal case by Swift and associates.[13] Twelve of the 25, as well as the one case in an adult, ended fatally.

CASE REPORT

D. J., a 29 mo. old white male, was found eating ferrous sulfate tablets. He was seen by another physician, who lavaged the stomach within ½ hr. after ingestion of the tablets. Patient was allowed to go home when a normal physical condition was determined. Physician did not know what amount of drug had been ingested.

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Submitted for publication with the approval of the Commanding Officer of the U. S. Naval Hospital, Key West, Fla. The opinions presented in the article are the author's and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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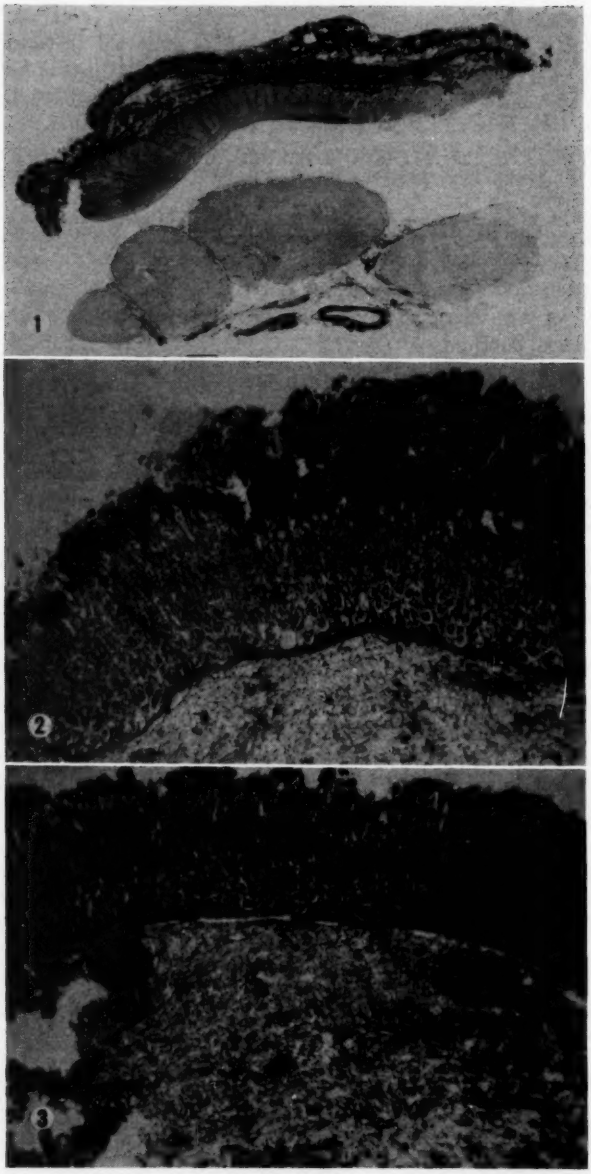

FIG. 1. Photomicrograph of stomach showing necrosis of ½ to ⅔ of gastric mucosa (iron stain). Iron is not demonstrable in lymph nodes. Iron is deposited in smooth muscle and connective tissue. Jejunum, ileum, colon and appendix showed superficial necrosis of mucosa.

FIG. 2. Higher power view of stomach seen in Fig. 1.

FIG. 3. Photomicrograph of stomach showing thrombosed veins in submucosa as well as necrosis of mucosa. (Hematoxylin and eosin stain.)

After the child returned home, vomiting, hematemesis and loose black stools appeared. Cyanosis was noticed about 1 hr. later. At time of admission to hospital (3½ hr. after ingestion of tablets) he was comatose and appeared moribund. There was no response to painful stimuli and no reflexes were present. Mucous membranes and nail beds were intensely cyanotic. Widely dilated pupils responded very sluggishly to light and corneal reflexes were absent. Respirations were fast, shallow and irregular. Heart beat was faint and irregular. The abdomen showed moderate distention, but no palpable organs or masses. Large brownish-black tarry stools were passed during examination.

Oxygen, external warmth, suction, intravenous fluids and blood were given as soon as possible. Death occurred 1 hr. after admission, 4½ hr. after ingestion of iron tablets. Blood studies for methemoglobin as well as other laboratory data were not obtained due to presence of extreme shock. Postmortem toxicologic studies showed no poisonous agents other than iron.

Recheck of history indicated that more than 60 and possibly up to 75 ferrous sulfate tablets (1.87 gm./kg. body weight) had been ingested. These 0.3 gm. tablets contained no other active ingredients.

Autopsy Findings*

Body was that of a well developed, and well nourished boy weighing 13.5 kg., and measuring 92 cm. in length. Cyanosis of head, shoulders, fingertips and toes was intense. Petechial hemorrhages were present over head, neck and chest. Edema of neck and generalized serous effusions were present. Marked pulmonary edema without infarction was present. Right side of heart showed acute dilatation. Hemorrhagic, necrotizing gastroenteritis involved stomach, small and large intestine, and even portions of appendix. Submucosal venous thromboses with iron pigment deposition were demonstrated in numerous areas of stomach. (See Figs. 1-3.)

Discussion

The history presented here of accidental ingestion of large amounts of iron by a small child is typical of most previous case reports. Characteristic vomiting, hematemesis, frequent tarry stools, vasomotor collapse, and cyanosis were present in this case. Part of the pathologic picture of pulmonary edema, acute dilatation of the right side of the heart, and edema of the neck may have been caused by intravenous fluids administered near and after death. The finding of hemorrhagic gastroenteritis with necrosis and slough has been recorded in most previous reports of iron poisoning. Gastric submucosal venous thromboses with iron pigment were demonstrated in this case.

It seems strange that a long and widely used drug such as ferrous sulfate had not been incriminated as an important poison until 1947. It is likely that other cases have been unrecognized or unreported.

Prevention of poisoning is paramount in therapy. The public, as well as all physicians, should be aware of the potential danger from ingestion of medication containing iron.

Thompson[5,6] found that emesis may rid the stomach of iron tablets even as late as one hour after ingestion. He believed that gastric lavage with bicarbonate solution converted the iron to the less irritating ferrous carbonate and also diluted the poison. Possibly feeding of raw eggs, milk or bismuth preparations would help protect the mucosa. Edge and Somers[14] found in work done on mice BAL-iron combinations to be more toxic than iron alone. Treatment of vascular collapse with blood, plasma and other fluid is important. The use of oxygen and other supportive measures is helpful.

Summary

A fatal case of ferrous sulfate poisoning in a 29 month old boy, with autopsy findings, is recorded. He died approximately 4½ hours after ingestion of about seventy-five 0.3 gm. ferrous sulfate tablets (1.87 gm./kg. body weight). Signs of severe gastrointestinal

* Autopsy performed by Lieutenant Commander C. G. Bratenahl, MC USN.

irritation were followed by cyanosis and peripheral vascular collapse. Hemorrhagic gastroenteritis with mucosal slough and submucosal venous thromboses were demonstrated post mortem. Prevention and measures for correction of shock were emphasized in discussion of treatment. This case report should re-emphasize the potential danger of iron poisoning.

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SPANISH ABSTRACT

Relato de un Caso Fatal de Intoxicación por Sulfato Ferroso

Se presenta un caso fatal de intoxicación por ingestión accidental de sulfato ferroso en un niño de 29 meses de edad. El enfermo murió a las 4½ horas aproximadamente después de la ingestión de cerca de 75 tabletas de 0.30 gramos de sulfato ferroso (1.87 gramos por kilo de peso corporal). Presentó síntomas de irritación gastrointestinal severa seguidos de cianosis y colapso vascular periférico, encontrándose histopatológicamente gastroenteritis hemorrágica con esfacelo de la mucosa y trombosis venosas submucosas.

Se enfatiza en el tratamiento el uso de sangre, plasma, líquidos, oxígeno, etc. para el colapso vascular y el peligro potencial de la intoxicación por hierro, debiendo prevenirse al público de esta eventualidad.

U. S. Naval Hospital

GIANT CELL PNEUMONIA WITH INCLUSIONS

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GIANT cell pneumonia has been described as an interstitial pneumonitis characterized by large multinucleated cells in alveoli, alveolar walls and bronchioles. These cells have prominent eosinophilic cytoplasmic inclusions and less prominent nuclear inclusions.

Clinically this pneumonia cannot be distinguished from other obscure subacute pneumonias and is seen in infants and young children. A specific virus has not been isolated. Most cases occur in association with syphilis, rubeola or tuberculosis.

Hecht[1] first described giant cell pneumonia in 1910 in 27 infants and young children. Karsner and Myers[2] reported a case associated with severe rickets and diffuse staphylococcal bronchopneumonia. Masson and Paré[3] reported a case of giant cell pneumonia associated with miliary tuberculosis and rickets. Chown[4] reported two cases, both infants with a history of congenital syphilis and one with bronchopneumonia, the other with rubeola. Pinkerton et al.[5] reviewed the literature in 1945 and reported two additional cases of their own. One was an infant with no other disease demonstrable and the other a 2½ year old child with pneumococcal pleuritis.

SUMMARY OF CLINICAL FINDINGS

Case #1893, a 9 mo. old white female infant, was admitted to a Philadelphia hospital where she was treated for severe tracheobronchitis, vomiting and fever. One day following admission she developed a paroxysmal whooping type of cough. She received parenteral penicillin therapy. She was transferred to the Philadelphia Hospital for Contagious Diseases 3 days later with a diagnosis of pertussis. No immunization history was obtainable.

Physical examination revealed bronchial rales throughout both lung fields and dullness over L base. Liver was palpated below R costal margin. She presented a typical whooping type of cough. Temperature was 38.8°C., respirations 40/min. and there was a purulent conjunctivitis and otitis.

After a few hours in hospital, temperature rose to 40°C. and during the next 8 days ranged from 37.8 to 40.5°C. There was slight cyanosis and blood pressure was 110/40 mm.Hg. She occasionally expectorated frothy pink sputum and was placed in an oxygen tent and given terramycin therapy orally.

Laboratory findings revealed a normal erythrocyte count and a leukocyte count of 30.7 M/m³ with 29% neutrophils and 71% lymphocytes. Spinal fluid examination revealed 22 lymphocytes/m³ fluid. Throat culture on day of admission revealed Staph. albus and H. influenzae, but all studies were negative for pertussis organisms.

Her condition did not improve and on 3rd hospital day she became stuporous and fluids were administered by clysis. Chest roentgenogram revealed some mottling with increased density of L lung base just above the diaphragm interpreted as pneumonitis (Fig. 1).

Paroxysms of coughing continued and on 6th hospital day it was noted that cyanosis and apnea often followed the cough. She was given antipertussis rabbit serum. She died on 8th hospital day.

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FIG. 1. Roentgenogram showing increased densities in lung fields.

FIG. 2. Lung with small bronchus showing severity of pneumonitis. × 100.

FIG. 3. Lung with small bronchus showing severity of pneumonitis. × 100.

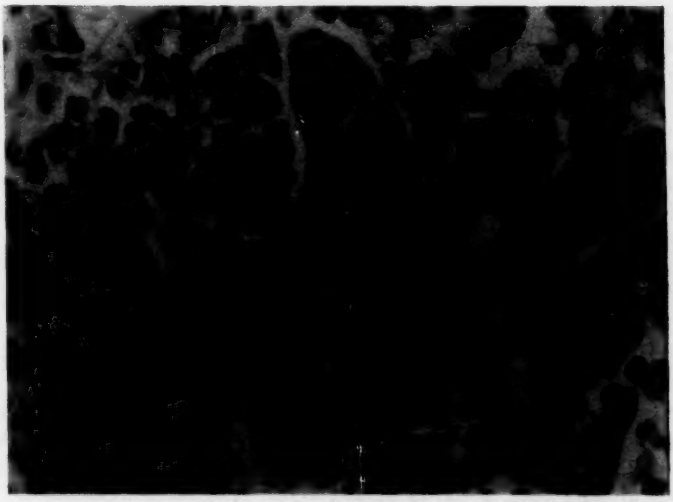

FIG. 4. Higher magnification of Fig. 3 revealing prominent cytoplasmic inclusions, with halos, in giant cells.

Summary of Autopsy Findings

Autopsy examination was performed 15½ hr. after death. Lips and nail beds were cyanotic. Heart muscle was pale with fair tone. Both lungs revealed smooth, thin pleurae. Left lung weighed 120 gm. and right lung 100 gm. Cut section of R lung revealed dark red foci of consolidation with surrounding reddish pink moderately spongy parenchyma. Apical and medial portions of L upper lobe were similarly consolidated. Tracheobronchial mucosa was hyperemic and smaller bronchial branches contained grayish yellow mucoid material.

Liver was pale yellow brown and weighed 625 gm. Parenchyma was moderately softened. Spleen and kidneys were moderately congested and kidneys were pale pinkish gray and slightly softened. Thymus was moderately decreased in size. Examination of central nervous system was not permitted.

Microscopic examination of lungs revealed numerous foci of consolidation with almost complete destruction of small bronchi, the lumina of which were filled with exudate consisting of large phagocytes, multinucleated giant cells, polymorphonuclear leukocytes, fibrin and some erythrocytes. Similar exudate was present in walls of bronchi which are partially destroyed (Fig. 2) and also found in alveoli (Fig. 3). In some areas small abscesses were seen which were made up of polymorphonuclear leukocytes and cell debris. Throughout the exudate were numerous giant cells containing deep red, well circumscribed, prominent cytoplasmic inclusions, often surrounded by a halo (Fig. 4). Intranuclear inclusions were also present, but these are less prominent. Inclusions were also seen in the bronchial epithelium and alveolar lining cells. Gram stain for bacteria was negative.

Spleen was congested and many neutrophilic leukocytes were present in pulp and sinuses. Some larger mononuclear cells were also noted. Normal liver architecture was distorted due to numerous large fat vacuoles within liver cells in all portions of lobules. These vacuoles almost competely replaced the cytoplasm.

There was some cloudy swelling of renal tubular epithelium. Remainder of viscera revealed no remarkable microscopic findings. It may be noted that no inclusions were found in viscera, other than the lungs after diligent search.

Discussion

Several types of viral pneumonia with inclusions are to be differentiated from the pneumonia described here. Adams[6] described a viral pneumonia in infants in which there are cytoplasmic inclusions, but no giant cells and no nuclear inclusions. The cytoplasmic inclusions are also smaller than those seen in giant cell pneumonitis. Milles[7] reported two cases of measles bronchopneumonia in adults but did not describe inclusions within the giant cells. Denton[8] reported six fatal cases of rubeola during an epidemic and in two of these cases a giant cell pneumonia was present with nuclear and cytoplasmic inclusions. The findings in these two cases were indistinguishable from the pneumonia described here.

The large eosinophilic nuclear inclusions and small basophilic cytoplasmic inclusions in inclusion-disease pneumonitis appear to be distinctly different from the case reported herein.

The viral pneumonia of infants described by Goodpasture et al.[9] does not show giant cells or cytoplasmic inclusions.

Pinkerton et al.[5] reviewed the findings from Chown's[4] cases and found the typical inclusions in giant cells of one case and giant cells without inclusions in the second case. The slides from Karsner and Myers'[2] case, also on being reviewed, revealed typical inclusions in giant cells in the lungs and a few cytoplasmic inclusions in bile duct epithelium.

Since surprisingly few cases have been reported and since Pinkerton et al.[5] were the first to draw attention to the inclusions in this disease as well as to the striking similarity of pulmonary lesions seen in canine distemper, it is felt that attention should again be called to this disorder.

Green and Evans,[10] among others, described the inclusions of distemper in 1939. In distemper, inclusions are commonly seen in the cells of other viscera, but in giant cell pneumonia this finding is uncommon. In one case reported by Pinkerton et al.[5] inclusions were found in reticuloendothelial cells of the spleen similar to those seen in distemper and, as previously noted, in the bile duct epithelium of the case reported by Karsner and Myers.

Taskin[11] believed that man is an asymptomatic carrier of the distemper virus for the dog. It is also interesting to note that Eichorn and Pyle[12] reported a cross-immunity between influenza and distemper.

The present author feels that this disease is worthy of reporting for the following reasons: 1. No report of cases associated with a disease clinically resembling pertussis could be found. 2. Few cases have been reported, although it would appear that this lesion should be seen more commonly. 3. It would appear that the lesion is of viral etiology and efforts should therefore be made toward isolation and study of this virus. Studies of pharyngeal smears or respiratory secretions may be of value in demonstrating inclusion bodies during life, as reported by Adams.[13] 4. It would be particularly interesting, in view of the histologic similarity of the pulmonary lesions, to study the relationship of this organism to the virus causing canine distemper.

Summary

A case of giant cell pneumonia with inclusions is reported. Intracytoplasmic and intranuclear inclusions are present. Exhaustive search reveals no inclusions in viscera other than the lungs. The pulmonary cytologic picture is similar to that seen in canine distemper.

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Spanish Abstract

Neumonía con Células Gigantes y Cuerpos de Inclusión

La neumonía con células gigantes ha sido descrita como una neumonitis intersticial caracterizada por la presencia de grandes células multinucleadas en los alveolos, paredes alveolares y bronquiales y

que muestran inclusiones eosinófilicas prominentes en el citoplasma y también en el núcleo, aunque menos aparentes. Clínicamente no puede ser diferenciada de otras neumonías subagudas obscuras y se ve en lactantes y niños pequeños, con mayor frecuencia asociada con sífilis, sarampión y tuberculosis. No se ha aislado ningún virus específico.

El autor reporta un caso en una niña de 9 meses con un cuadro severo de traqueobronquitis, vómitos y fiebre, que posteriormente desarrollo tos con caracter típicamente tosferinoso, presentando estertores bronquiales diseminados en ambos campos pulmonares y macicez en base izquierda. Simultáneamente tuvo conjuntivitis purulenta y otitis.

Evolucionó con hipertermia, cianosis, expectoración ocasionalmente, con caracter espumoso, color rosado; cayo en estupor al tercer día de internada y los paroxismos de tos continuaron, presentando en los últimos días cianosis y apnea después de ellos. Murió a los 8 días a pesar de penicilina, terramicina, suero antitosferinoso de conejo, oxígeno, etc. Radiológicamente se encontró moteado y aumento de la densidad en la base izquierda que se interpretó como neumonitis. Tuvo leucocitosis de 30.700 con 29% de neutrófilos y 71% de linfocitos. El líquido cefalorraquídeo presentó 22 linfocitos por mm^3 y en los cultivos de exudado faríngeo se aisló estafilococus albus y bacilo hemofilus influenza pero todos los estudios fueron negativos para el hemofilus pertusis.

El examen microscópico de los pulmones reveló numerosos focos de consolidación con destrucción casi completamente de los bronquiolos, que aparecían llenos de exudado con grandes fagocitos, células gigantes multinucleadas, polimorfonucleares, fibrina y algunos eritrocitos. Las células gitantes contenían inclusiones citoplásmicas prominentes, bien circunscritas, de color rojo intenso, a veces rodeadas de un halo. Igualmente estas inclusiones, aunque menos definidas se veían dentró de los nucleos. Estos cuerpos de inclusión también se apreciaban en el epitelio bronquial y las células alveolares de revestimiento pero su búsqueda minuciosa en el resto de las vísceras fué negativa.

Estas lesiones pulmonares son similares a las del moquillo o gripa del perro.

El autor cree que es importante reportar la enfermedad por las siguientes razones: no encontró reportes de otros casos asociados con un proceso que clínicamente semeja a la tosferina, porque es posible que sea mas frecuente aunque pocos casos se han publicado, parece ser que su etiología es viral y deben de hacerse intentos de aislar y estudiar el virus y finalmente debe estudiarse la relación de este virus con el que causa la gripa o moquillo canino.

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ANOMALIES OCCURRING IN CHILDREN EXPOSED *IN UTERO* TO THE ATOMIC BOMB IN HIROSHIMA

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THE development of congenital anomalies in the fetus following therapeutic x-ray radiation to the gravid maternal pelvis has been well known for many years.[1] The present report is concerned with the occurrence of congenital anomalies in a group of infants exposed during the first 20 weeks of gestation to the radiation from the atomic bomb exploded in Hiroshima, Japan, on August 6, 1945.

MATERIALS AND METHODS

Children born between January 1, 1946, and May 1, 1946, of mothers who had been within the city limits of Hiroshima at the time of the atomic bomb explosion and still surviving at 4½ yr. of age were designated for this study. This span of birth dates was chosen to obtain information on all children who had been in the first trimester of intra-uterine life at the time of the atomic bomb blast. A total of 205 such children were discovered and studied in the summer and autumn of 1950.

A history was obtained on each mother and child by a Japanese physician. Information on the mother included history of injuries and burns at the time of the atomic explosion; symptoms occurring after the blast which are suggestive of radiation illness (epilation, purpura, fever, vomiting, diarrhea, gingival bleeding and oropharyngeal lesions); termination of previous pregnancies and occurrence of anomalies, including specific information regarding the course and termination of the pregnancy under investigation; location of the mother with regard to distance and direction from the hypocenter of the atomic bomb.

A routine pediatric history obtained on each infant included family history, birth, neonatal, nutrition, growth and development and system review information. A complete physical examination was made by an American pediatrician at the ABCC Clinic when the child was 4½ yr. of age. Anthropometric data, including height, weight and head circumference, were obtained, together with an estimation of mental development made by a Japanese physician; also laboratory studies, including complete blood count, urinalysis, serologic test for syphilis, stool examination for parasites and chest RG. No control children were studied at the time this investigation was carried out; however, paired controls have been selected since, and yearly examinations of both groups are being performed. The analyses and comparative results of these subsequent examinations will be the subject of a separate report.

RESULTS

Table 1 demonstrates the distribution of these 205 pregnant women by distance in meters from the hypocenter of the atomic bomb explosion and also lists the number of times various symptoms were recorded at each distance. It is noteworthy that only 11 (5%) were within 1200 meters of the hypocenter.

A history of burns, injury, epilation, purpura, fever or G.I. tract bleeding was recorded 101 times in 68 women; 20 of these women had multiple symptoms. Injury accounted for 52 of the 101 symptoms, of which 33 were classified as slight.

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TABLE 1

DISTRIBUTION OF MOTHERS OF CHILDREN *In Utero* DURING ATOMIC BOMBING BY DISTANCE FROM HYPOCENTER AND SYMPTOMS OF RADIATION EFFECT AT EACH DISTANCE

Distance in Meters from Hypocenter	No. of Women	No. and Type of Symptoms at Each Distance						
		Burn	Injury	Epilation	Purpura	Fever	GI Tract Bleeding	Total
Under 1000	4	2	2	4	3	2	1	14
1000–1199	7	2	4	2	2	3	1	14
1200–1399	16	2	7	2	0	1	2	14
1400–1599	8	0	5	0	0	0	1	6
1600–1799	14	0	5	0	0	0	2	7
1800–1999	11	2	3	0	0	1	0	6
2000–2499	41	5	16	0	0	3	2	26
2500–2999	24	2	4	0	0	0	0	6
3000 and over	80	1	6	0	0	0	1	8
Total	205	16	52	8	5	10	10	101

68 women gave a history of 101 symptoms.

It is the consensus of the members of the Commission that the most reliable symptoms of radiation effect obtained from histories are epilation and purpura. In the present series, 8 women, all of whom were within 1400 meters, gave a history of epilation; 5, all of whom were within 1200 meters, had purpura. It is apparent, therefore, that persons within 1400 meters of the hypocenter have the greatest likelihood of sustaining serious radiation injury. The other physical factor which must be considered is the amount of shielding, such as buildings, walls, fences and topography, which may protect the individual from the

TABLE 2

CONGENITAL ANOMALIES FOUND AMONG 205 CHILDREN EXPOSED TO ATOMIC BOMB BLAST WHILE *In Utero*

Anomaly	No.	Distance of Mother from Hypocenter
Microcephaly with Mental Retardation	6	All under 1200 m.
Mongolism	2	One under 1200 m. One between 2500 and 3000 m.
Congenital Dislocation of Hips	4	One under 1000 m. (also was microencephalic) One between 1600 and 1800 m. Two over 2500 m.
Congenital Heart Disease	3	All questionable and all over 3000 m.
Hydrocele	2	Both over 2000 m.
Funnel Chest	1	Between 1200 and 1400 m.
Calcaneo Valgus	1	Over 3000 m.
Deformed Iris	1	Between 1600–1800 m.
Deformed Ear (hereditary)	1	Over 3000 m.
Congenital Strabismus	1	Over 3000 m.
Congenital Glaucoma	1	Over 2000 m.
Partial Albinism	1	1600 m.
Total	28	

radioactive energy. This shielding factor will be discussed in more detail later.

Congenital Anomalies: Table 2 lists the anomalies which were discovered in the course of examining the 205 children and records the distance of the mother from the hypocenter in each instance.

Microcephaly with mental retardation was the most frequent anomaly. This diagnosis was made six times and all the cases were exposed within 1200 meters of the hypocenter. The two cases of mongolism are interesting in that one who was exposed beyond 2500 meters had a normal head size, whereas the one exposed within 1200 meters had microcephaly. Seven out of 11 mothers within 1200 meters of the hypocenter were delivered of children diagnosed as having microcephaly and mental retardation. This high incidence

TABLE 3

CASES EXPOSED *In Utero* WITHIN 1200 M. OF ATOMIC BOMB HYPOCENTER

Case No.	Distance of Mother from Hypocenter	Mother's Age at A Bomb Blast	History of Epilation	Purpura	Weeks of Gestation at A Bomb Blast	Sex of Child	Head Circumference (cm.)	Mental Development of Child	Nonmedical Radiation History
39	950 m.	27	75%	—	6	M	50.5	Normal	Standing outside partially shielded by concrete wall
121	930 m.	23	25%	—	12	M	40.5	Retarded	Standing near open window
125	1110 m.	43	Slight ?	Slight ?	15	F	43.4	Retarded Mongolism	Sitting inside shielded by mud wall
127	730 m.	24	100%	—	14	F	38.4	Retarded	Standing near open window
131	1040 m.	32	100%	—	11	F	43.3	Retarded	Standing outside—no shielding
147	1130 m.	25	0	—	16	F	46.3	Normal	Sitting on roka at far end of house from blast
178	1050 m.	38	Mod.	0	12	M	44.3	Retarded	Standing outside—slight shielding
182	1190 m.	29	0	0	9	M	49.0	Normal	Standing outside—shielded by concrete building
200	720 m.	23	100%	0	12	F	43.6*	Retarded	Standing outside—shielded by wooden building
201	1150 m.	37	?	0	17	M	45.6	Retarded	Sitting inside—shielded only by lattice door
115	1120 m.	25	0	0	7	F	43.3	Normal	Standing in front of window

* Measurements at 5 yr.; others are at 4½ yr.

is unquestionably significant when it is contrasted to the absence of microcephaly among the 194 cases who were exposed at distances greater than 1200 meters.

Microcephaly is the only congenital defect with demonstrable correlation with distance of the mother from the hypocenter. The other anomalies were widely scattered as to distance from the hypocenter, and the incidences of the individual anomalies were similar to those found in studies on other populations in Japan. There was no correlation demonstrable between any of the anomalies and such factors as mother's age, birth order, or week of gestation at the time of A-bombing.

Cases Exposed Within 1200 Meters: Table 3 lists the pertinent data on each of the 11 cases who were exposed within 1200 meters. The distances of these cases from the hypocenter are well scattered between 720 and 1190 meters. The mothers' ages ranged between 23 and 43 years; 3 were over 36 years. The distributions of the mothers' ages in the total series of 205 mothers showed that 75% were within the age range of 21 to 36. The week of gestation at the time of the atomic bomb blast is noted for each case; 8 of the 11 were in the third and fourth lunar months. The distribution by time of gesta-

tion of the 205 women revealed 63% of them to be in the third and fourth lunar months. Sex distribution for the children in this group is comparable to that for the total which was 104 males to 101 females.

The head circumference measurements on the 11 4½ year old children contributed the most revealing data. The mean head circumference for 4 to 5 year old Japanese children found in tables published by the Japanese Ministry of Welfare in 1951 is 50.2 ±1.64 cm. for boys and 49.3 ±1.69 cm. for girls. Only 2 of these 11 children fell within 1 standard deviation of these means. One other child had a head circumference within minus 3 standard deviations of these means. All the rest had head sizes at 4½ years which are below the Japanese mean circumferences of 47 ± 1.83 cm. for boys and 46.1 ±1.63 cm. for girls at one year of age. The mean head circumference for 171 of the 205 children is 48.6 ±1.3 cm. These 171 include all who had head circumferences measured except those whose measurements were below 45 cm.; all with circumferences smaller than 45 cm. were within 1200 meters of the hypocenter.

The three children with normal head circumferences in this group merit some discussion with respect to the mothers' radiation symptoms and to the shielding afforded the mother by virtue of her location at the time of the atomic blast. Case 39, as presented in table 3, was standing 950 meters from the hypocenter and was partially shielded by a concrete wall 4 meters high which was 13 meters from her position. However, by a geometric reconstruction showing the mother's position, the location and height of the wall, the location and height of the bomb blast, it is evident that the wall afforded no shielding whatever. This is borne out by the fact that she experienced 75% epilation and purpura following the bomb explosion. There is a possible explanation of the normal head size and development of this child: His mother was in the sixth week of gestation at the time of exposure, an earlier period in pregnancy than the other women in this heavily-radiated group. Hicks[2] has demonstrated a critical period in gestation for the production of nervous system defects by radioactive materials in fetal rats. He found that radiation of the gravid rat during the first eight days of pregnancy produced no nervous system malformation, whereas severe malformations were found when the radioactive insult occurred on the ninth and subsequent days of gestation. There is a possibility that such a critical period exists for humans and that the present case was exposed prior to that stage of his development.

Case 147 was sitting on a roka (narrow platform which extends around the outside of Japanese dwellings) at the far end of the house from the hypocenter at a distance of 1180 meters. The mother experienced some purpura but no epilation. Her child's development was normal and the head size was low normal. The shielding in this case consisted of several thicknesses of wooden walls.

Case 182 was standing outside at a distance of 1190 meters, completely shielded by a concrete building. She experienced neither epilation nor purpura, and her child's head size and development were normal. The eight other mothers were either outside with little shielding or inside in front of open windows or protected by only a single door or wall.

Case 115 is interesting in that his development was apparently within normal limits in spite of an unusually small head circumference (43.3 cm.). The mother of this child experienced neither epilation nor purpura, although she was standing in front of an open window facing the blast at a distance of 1120 meters.

Discussion

The relationship between the occurrence of microcephaly and x-irradiation during intra-uterine life has been recognized for many years. Murphy,[1] however, probably was the first to focus sharp attention on this phenomenon. He studied a group of 75 children who had been irradiated while *in utero* during the course of radium or roentgen ray therapy to the mother's pelvis. Sixteen microcephalic children were found among this group of 75. Four other children exhibited other central nervous system defects. An additional eight children exhibited other anomalies or disturbances of health, which makes a total of 28 children out of 75 who suffered defects attributable to irradiation during fetal life. The dosages of roentgen ray were not known for this group, but one child with microcephalic idiocy had been exposed to 4400 mg. hours of radium therapy while *in utero*. The time of treatment in pregnancy in Murphy's tables is broken down to only "before 5 months" and "after 5 months." Two children with microcephaly had been irradiated after five months; the other 14 were irradiated during the first half of gestation.

Hicks's investigation[2] on x-irradiated fetal rats demonstrates a marked susceptibility of neuroblasts to radioactive insult. He found, as mentioned above, that no nervous system defects occurred if the gravid rat was irradiated with dosages up to 300 r the first 8 days of its 21 day gestational period. Irradiation of 150 r on the ninth and tenth days produced anencephaly and encephaloceles; irradiation on later days produced forebrain defects; and irradiation late in gestation and early in the newborn period produced cerebellar defects. Hicks's explanation of the absence of effect of irradiation during the first eight days is that during this period the rat's central nervous system is composed of radio-resistant primitive neuroectoderm and that differentiation of the neuroectoderm and proliferation of radiosensitive neuroblasts does not occur until the ninth day of fetal life.

The results of the present study demonstrate that a fetus *in utero* may receive sufficient radioactive radiation from an atomic bomb explosion to produce central nervous system defects if the mother is within approximately 1200 meters of the explosion and is not well shielded. The only shielding in the present study which apparently was effective in protecting against irradiation was concrete. Single wooden and mud walls were not effective shields. The problems of radioactive back-scatter and residual radiation do not appear relevant to the discussion in the present study. The role of individual biologic resistance to radiation could not be determined from this study.

The relationship of period of gestation to susceptibility of the developing human central nervous system to irradiation is not clearly defined by this study, although in the only instance in the heavily-irradiated group with epilation and purpura where the gestation period was as short as six weeks, no defect was discernible in the child. This suggests the possibility that the nervous system of the human may be resistant to radioactive material in its early stages of development, but no conclusions can be based on one case.

Comment

The design of this study was such that the source of material was limited to children exposed during the first half of intra-uterine life to the atomic bomb blast who were still surviving at 4½ years of age. This method obviously leaves large gaps in a complete study of the effect of irradiation on pregnancy. The cases omitted by virtue of this design are those which resulted in abortions, stillbirths and neonatal and infantile deaths. The probability is great that some heavily irradiated fetuses *in utero* were so severely damaged

that death occurred either prior to term or during early postnatal life. Another group of cases missed by this study is that in which exposure to the atomic bomb blast occurred during the latter part of intra-uterine life. It is evident from Murphy's work[1] and from Hicks's animal studies[2] that central nervous system damages can occur following irradiation during later *in utero* existence. A study designed to include the above groups of cases should have as its source of material all pregnant women who were exposed to the atomic bomb blast.*

Summary and Conclusions

A study was carried out on 205 4½ year old children who had been exposed to the atomic bomb blast during the first half of intra-uterine life. Eleven were exposed within 1200 meters of the bomb hypocenter, and the remaining 194 were beyond this distance.

Seven of these 11 children exposed within 1200 meters had microcephaly with mental retardation. This diagnosis was not made on any of the 194 children exposed at greater distances.

Correlation between head size and mental development of the child with distance from the hypocenter, symptoms of radiation effect and type of shielding of the mother is discussed.

The conclusion drawn from the present study is that central nervous system defects can be produced in the fetus by atomic bomb radiation, provided that exposure occurs within approximately 1200 meters of the hypocenter and that no effective shielding, such as concrete, protects the fetus from direct irradiation.†

Acknowledgments

The author is indebted to Dr. Jane Borges who, early in the ABCC Pediatrics program, was impressed with the frequency of microcephaly among the infants in this study. The splendid work of Dr. Wataru W. Sutow and Dr. John Wood of the American Pediatrics Staff is gratefully acknowledged, as is the assistance of a number of other members of the Commission, both Japanese and Americans.

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Spanish Abstract

Malformaciones Ocurridas en Niños Expuestos in Utero a la Bomba Atómica en Hiroshima

El presente estudio se refiere al desarrollo de malformaciones congénitas en un grupo de 205 niños de 4½ años de edad que fueron expuestos durante las primeras 20 semanas de vida intrauterina a las radiaciones de la bomba Atómica que hizo explosión en la ciudad de Hiroshima, Japón, el 6 de Agosto de 1945.

Se hizo una historia detenida de cada madre acerca de las lesiones sufridas durante y después de la explosión atómica sugestivas de enfermedad por radiación (depilación, púrpura, fiebre, vómito,

* A study designed in this way has been carried out in Nagasaki by the Atomic Bomb Casualty Commission and the results are presently being analyzed.

† It is impossible to publish accurate radiation dosage data for the exposed mothers because this is restricted material. Obviously the dosage range must have been high to produce epilation and purpuric phenomena.—Committee on Atomic Bomb Casualties, National Academy of Sciences.

diarrea, hemorragia gingival y lesiones orofaringeas), final de los embarazos anteriores, frecuencia de malformaciones, incluyendo información específica en relación con el curso y terminación del embarazo en investigación, situación de la madre con respecto a la distancia y dirección del hipocentro de la bomba Atómica.

Igualmente se le hizo a cada niño una historia clínica de rutina incluyendo antropometría, exámenes de laboratorio de rutina y una estimación de su desarrollo mental.

Once de los niños fueron expuestos a la radiación dentro de los 1200 metros del hipocentro de la bomba, y los 194 restantes estaban mas allá de dicha distancia. Siete de los 11 niños citados eran microcefálicos con retardo mental, en cambio, no hubo ningún caso con dicho diagnóstico entre el grupo de los 194 niños que se encontraban a mayor distancia.

Aun cuando en este último grupo hubo otras malformaciones, la microcefalia fué la única que demostró correlación con la distancia entre la madre y el hipocentro.

Murphy, en un grupo de 75 niños que habían sido irradiados in utero durante terapia de radio o rayos X de las pelvis maternas encontró 16 niños microcefálicos, cuatro de los cuales tenían además otras anomalias del sistema nervioso central y 8 mas presentaban otro tipo de anomalías o procesos patológicos, haciendo un total de 28 niños afectados por la radiación. De los 16 microcefálicos, 14 fueron irradiados en su vida intrauterina antes de los 5 meses y los otros después. Hick, encontró que no se desarrollaban anomalías del sistema nervioso en los productos de ratas cuando éstas se radiaban durante los primeros 8 días de su primer periodo de gestación de 21 días y en cambio se producía anencefalia y encefaloceles si aún con la mitad de la dosis se hacía la radiación en el 9° y 10° días, dando defectos del encéfalo y cerebelosos si la radiación se hacía mas tardíamente, explicando la ausencia de efecto de radiación en los primeros 8 días porque durante dicho período el sistema nervioso central de la rata está formado por el neuroectodermo primitivo que es radioresistente y que su diferenciación y proliferación de neuroblastos radiosensibles no ocurre sino hasta el 9° día de la vida fetal.

La relación entre el período del embarazo y la susceptibilidad del sístema nervioso central humano a la radiación no se define claramente en este estudio, aunque en el único caso del grupo de madres que fueron radiadas intensamente presentando depilación y púrpura, cuando el tiempo de embarazo era de 6 semanas, no se descubrió defecto alguno en el niño, sugiriendo la posibilidad de que en esa época el sistema nervioso del hombre pueda ser resistente a los elementos radioactivos.

Sin embargo, no pueden sacarse conclusions basadas en un solo caso. Por consiguiente, la única conclusión definitiva de este estudio es de que pueden producirse anomalías del sistema nervioso central del feto por medio de la radiación de la Bomba Atómica, cuando la distancia de la madre embarazada al hipocentro es menor de 1200 metros aproximadamente y siempre y cuando no haya protección efectiva, como concreto, que defienda al feto de la radiación.

Atomic Bomb Casualty Commission

ALTERATIONS IN BLOOD CHEMISTRY CAUSED BY DIARRHEA DURING INFANCY AS DETERMINED BY DIRECT ANALYSIS OF PLASMA AND ERYTHROCYTES

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THE present concept of the chemical alterations which occur in the various body fluids during states of dehydration with acidosis or alkalosis, due to diarrhea, vomiting, diabetes, etc., is familiar to students of fluid and electrolyte balance. References cited in the review articles of Guest,[1] Darrow[2, 3] and Butler[4] are complete and accurate summaries. The exchange of inorganic ions across the cell membrane and the subsequent loss of these ions from the body has been demonstrated by the earlier work of Darrow,[5, 6] Darrow, Pratt, Flett and Gamble,[7] Gamble et al.[8] and Holler[9] as well as others, by means of balance studies, the complexity of which restricts their use in clinical medicine. For this reason a study involving the chemical and physical-chemical determination of the major plasma and erythrocyte ions during diarrhea seems indicated.

CLINICAL MATERIAL

Forty-two infants between the ages of 2 and 15 mo. who were sufficiently ill and dehydrated because of diarrhea to require hospitalization were included in this study. Duration of illness prior to hospitalization ranged from 2 to 7 days. Accurate information as to the frequency of stools was difficult to obtain; however, it was not unusual to obtain a history of 15 to 18 liquid stools during 24 hr. preceding admission to hospital. Vomiting was present in 76% of the cases and fever in 80%. Tissue turgor was poor in all cases and Kussmaul breathing was uniformly present.

METHODS

Soon after admission and before any treatment was administered venous blood was obtained under oil from the femoral or jugular vein. Analyses were made on heparinized plasma for Na, K, Ca, Cl, CO_2 content and protein. Erythrocytes were separated from plasma by centrifugation at 3000 rpm for 45 min. and analyzed for Na, K and Cl in a manner identical with that used for their determination in normal infants.[10] Plasma inclusion following such a procedure has been observed not to exceed 1.6%. In the case of Na a plasma inclusion of 0.87% to 1.6% would influence the erythrocyte value from 1.2 to not more than 2.2 mEq./l.; Cl and especially K obviously would be influenced to a lesser degree. NPN was determined on whole blood. Sodium and potassium concentrations were determined by use of a Model 52-A Perkin-Elmer internal standard flamephotometer.[10] Ca was determined by Clark-Collip modification of the Kramer-Tisdall method.[11] Cl was measured by a modification of Volhard method,[12] care being taken to exclude contact with air in order to prevent the "chloride shift." CO_2 content was determined by manometric method of Van Slyke.[13] Plasma protein concentration was determined by copper sulfate method of Phillips[14] and by micromethod of Weichselbaum[15] and NPN was determined by micro-Kjeldahl method of Folin-Wu.[16] Hematocrit was measured by Wintrobe method with centrifugation at 3000 rpm for 45 min.

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Results

Table 1 gives the chemical data obtained from individual patients arranged in order of increasing age. In table 2 the patients are classified into age groups and the mean, range and standard deviation of the mean for each variable is presented in a manner similar to that used for previously published data on normal infants.[10]

The critical ratio* has been calculated for the different variables in each age group and will be referred to from time to time.

Plasma Na was usually decreased as a result of diarrhea with the exception of the group between 11 and 15 months of age. Approximately 80% of the patients in the three younger age groups had plasma sodium levels below the mean for normal infants and 63 to 80% of these patients had levels below the lower limits for normal infants of similar ages. A critical ratio of 2.4 was obtained for the 8 through 10 months-of-age group which represents a significant decrease at the 5% level. The critical ratio for the 2 through 4 months and the 5 through 8 months age groups was 1.6 and 1.8, respectively, which is significant only at the 10% level. In the 11 through 15 months age group the mean value was slightly less than the mean obtained for normal children of a similar age; a critical ratio of 0.66 indicates that no significance can be attached to alterations of this magnitude. In only three instances was the plasma Na observed to be greater than one standard deviation above the mean for normal infants.

Plasma K in the majority of instances was reduced below the mean value for normal infants (tables 1 and 2) with 50, 75, 78 and 100% of the individual cases of the various groups arranged in order of advancing age having had plasma potassium levels below the mean for normal infants. In 20, 25, 55 and 57% of the cases of each group, the plasma K fell below the range for normal infants of similar ages. Upon statistical analysis, however, a critical ratio not exceeding 1.73 indicated an insignificant alteration in the plasma concentration of the ion.

There were only four patients in the entire series (tables 1 and 2) in whom the plasma potassium levels exceeded one standard deviation above the mean for normals, with the highest value recorded being 6.3 mEq./l.

The authors did not observe plasma potassium levels as high as those reported by Darrow et al.[5,7] nor as low as those reported by Gamble, Wiese and Hansen.[17] The greatest and most consistent decrease in this ion was observed in the older group of infants between 11 and 15 months of age. This was not altogether anticipated since the greatest reduction in plasma sodium concentration occurred in the younger diarrhea patients in whom greater alterations in water and electrolytes are more prone to develop and kidney functions are more immature. It has not been possible to show any definite correlation between the plasma potassium level and the degree of acidosis.

Plasma calcium concentration was determined in 19 of the infants. There was practically no alteration in this ion when compared with the normal values.[10] The concentration ranged from 4.3 to 5.7 mEq./l. (table 1); a mean of 5.1 mEq./l. can be calculated

* Critical ratio = difference in means ÷ standard error of difference; standard error of difference was determined by formula,

$$\sqrt{\frac{(N_1+N_2)\cdot(\Sigma d_1^2+\Sigma d_2^2)}{N_1\cdot N_2[(N_1-1)+(N_2-1)]}}$$

in which N_1 is the number of determinations on normal children, N_2 number of determinations on patients with diarrhea, Σd_1^2 sum of squared deviations in normal group and Σd_2^2 sum of squared deviations in group with diarrhea.

TABLE 1

ANALYTIC DATA FROM INDIVIDUAL PATIENTS WITH DIARRHEA

Patient	Age	Wt.	Plasma					Erythrocyte			NPN	Plasma Prot.	Hct.
			Na	K	Ca	CO_2	Cl	Na	K	Cl			
	mo.	kg.	mEq./l.	mEq./l.	mEq./l.	mEq./l.	mEq./l.	mEq./l.	mEq./l.	mEq./l.	mg./100 cc.	gm./100 cc.	%
A.B.	2	2.7	126.5	4.1	—	4.5	116.0	20.1	80.2	—	64	6.9	38.7
B.H.	2	3.0	126.5	4.7	—	11.0	105.4	20.4	81.0	—	—	—	26.2
O.W.	2	4.5	132.1	4.1	—	8.2	99.4	20.8	85.9	—	—	—	—
H.H.	3	3.0	136.7	4.7	—	10.5	—	18.0	97.2	—	—	6.3	33.7
R.B.	3	5.2	129.9	2.7	—	10.0	—	23.6	97.4	—	32	—	42.2
J.H.	3	4.3	134.8	4.7	5.2	8.6	110.4	29.1	97.0	73.5	35	6.3	32.6
H.M.	3	4.5	150.4	4.6	—	11.4	—	—	—	—	—	—	47.7
F.S.	4	5.0	144.6	3.2	—	13.0	—	24.2	88.5	70.4	—	8.4	37.7
H.L.	4	5.8	132.1	5.6	—	17.7	98.0	19.7	99.0	56.6	70	—	—
J.B.	4	5.5	130.4	5.0	5.2	15.0	97.2	18.5	99.7	—	29	6.5	40.8
J.A.	5	5.2	120.4	6.3	5.0	15.5	83.7	13.3	87.2	52.4	—	—	36.0
J.J.	5	5.6	138.2	3.8	5.2	14.8	116.0	15.7	94.9	74.0	37	6.7	30.7
P.B.	5	5.6	125.4	4.9	—	18.1	94.1	21.7	93.6	53.8	—	7.0	52.0
C.B.	5	4.9	122.6	4.4	5.1	10.0	89.0	26.4	89.4	59.2	—	7.3	40.0
C.S.	5	4.6	151.7	4.2	4.3	4.1	112.7	29.1	97.0	73.5	53	5.9	34.9
E.K.	5	5.7	141.3	4.2	5.4	8.2	107.0	27.8	92.2	60.3	42	6.7	37.7
G.H.	5	5.6	119.4	2.7	—	6.6	99.7	14.6	92.3	—	—	6.3	40.0
J.C.	6	4.0	129.9	4.9	—	.6	98.0	25.0	91.0	67.0	—	6.7	29.6
H.P.	6	7.3	135.2	4.4	—	9.3	102.8	15.2	94.3	62.5	98	7.0	—
H.F.	6	6.3	128.9	3.0	5.9	11.0	98.6	21.5	90.4	57.8	47	7.8	37.9
J.W.	6	4.5	131.0	4.2	5.0	12.7	96.6	21.7	85.3	63.4	—	—	43.4
S.W.	6	6.9	138.2	3.7	5.2	15.2	101.7	22.6	89.7	54.1	34	6.7	37.9
W.F.	6	6.1	141.5	4.4	5.4	15.9	103.4	27.6	94.8	69.6	45	6.7	34.0
J.B.	7	6.0	129.9	3.7	—	16.4	90.4	16.8	93.1	—	60	—	44.1
J.H.	7	5.9	127.8	4.5	5.2	23.1	90.0	16.7	98.1	—	—	7.4	43.6
W.P.	7	7.8	138.2	4.1	—	6.8	105.0	14.8	100.0	68.7	—	8.2	38.2
E.G.	8	5.5	135.2	4.9	—	8.6	99.4	21.7	89.7	59.7	—	7.7	39.8
J.W.	8	4.0	140.0	2.8	—	6.4	105.6	19.1	104.0	69.9	36	6.5	29.3
S.E.	8	6.3	130.4	4.8	—	16.0	89.6	17.2	95.4	59.2	75	—	42.3
C.W.	8	8.1	141.5	3.8	5.6	21.8	104.8	28.4	98.8	69.2	42	5.7	29.6
D.B.	9	8.2	127.8	4.1	—	13.2	94.9	20.2	84.6	53.5	—	7.5	33.2
J.M.	9	7.8	133.7	2.9	5.0	7.7	103.7	13.3	95.6	68.7	77	7.5	35.3
T.B.	9	7.4	128.9	3.4	—	13.0	106.8	30.5	86.2	69.9	39	7.8	37.9
R.H.	10	6.3	126.3	3.5	4.8	18.4	92.7	17.0	105.2	50.7	32	6.3	34.7
D.M.	10	7.3	131.0	4.4	—	16.0	89.5	16.5	97.9	—	54	—	42.0
J.S.	11	8.3	129.9	3.9	—	16.0	98.0	34.3	85.9	—	37	6.2	26.0
N.R.	11	6.6	132.1	3.5	—	16.0	102.8	20.7	106.0	—	36	6.3	26.2
R.H.	12	5.5	141.7	3.3	4.8	17.5	116.3	25.0	104.0	76.9	39	7.5	25.7
Q.S.	12	9.7	140.0	3.6	5.2	20.0	109.3	20.2	100.0	68.7	31	7.0	—
L.B.	12	10.2	138.2	3.8	4.6	17.5	102.8	26.2	100.0	64.8	35	6.3	29.0
D.C.	15	6.7	138.2	2.9	5.2	22.3	106.0	15.9	105.0	69.9	31	7.0	31.4
M.H.	15	8.2	139.1	4.0	—	7.3	101.0	14.8	105.0	60.3	—	7.5	37.0

from these data. The number of determinations was insufficient to permit grouping of the data according to age or subjecting them to statistical analysis.

Plasma chloride concentration showed wide individual variations as in normal infants (tables 1 and 2). The changes in the mean plasma chloride level in the patients with diarrhea were similar to the changes in the mean plasma sodium concentration.

Plasma HCO_3 was uniformly and significantly decreased. All the patients (100%) in the 2 to 4 month age group and 94, 89 and 71% of the patients in the remaining groups arranged in order of advancing age had a plasma bicarbonate concentration below the range for normal children. The critical ratios for the various groups ranged from 3.1 to 5.6 which represent highly significant decreases. These observations illustrate the tendency for a more serious acidosis to develop in the younger patients in whom homeostatic mechanisms function less efficiently. The authors observed that the clinical

TABLE 2

MEAN, RANGE AND STANDARD DEVIATION OF MEAN FOR VARIOUS PLASMA AND ERYTHROCYTE, IONS, ETC., FOR NORMAL INFANTS AND INFANTS WITH DIARRHEA, GROUPED ACCORDING TO AGE

Variable	Normal 2–4 mo.	Diarrhea 2–4 mo.	Normal 5–7 mo.	Diarrhea 5–7 mo.	Normal 8–10 mo.	Diarrhea 8–10 mo.	Normal 11–15 mo.	Diarrhea 11–15 mo.
No. cases	16	10	16	16	12	9	15	7
Plasma Na								
Mean	142.0	134.4	141.0	132.5	140.0	132.8	139.0	137.0
Range	137.0–153.0	126.5–150.4	137.0–155.0	119.4–151.7	138.0–142.0	126.3–141.5	135.0–144.0	129.9–141.7
S.D. Mean	±4.3	±2.32	±4.2	±2.14	±2.4	±1.67	±2.6	±1.52
Plasma K								
Mean	4.7	4.3	4.5	4.2	4.5	3.8	4.6	3.6
Range	4.0–5.4	2.7–5.6	3.8–5.3	2.7–6.3	4.1–4.9	2.8–4.9	3.8–5.4	2.9–4.0
S.D. Mean	±0.40	±0.26	±0.48	±0.20	±0.26	±0.26	±0.47	±0.31
Plasma Cl								
Mean	106.0	104.4	105.0	99.3	103.0	98.6	104.0	105.2
Range	104.0–109.0	97.2–116.0	96.0–120.0	83.7–116.0	101.0–106.0	89.5–106.8	102.0–107.0	98.0–116.3
S.D. Mean	±1.6	±2.84	±5.0	±1.9	±1.9	±2.2	±2.4	±0.67
CO_2 Content								
Mean	23.6	11.0	24.6	12.3	24.1	13.5	24.0	16.6
Range	19.0–26.7	4.5–17.7	20.6–28.3	4.1–23.1	18.5–28.5	6.4–21.8	17.6–26.7	7.3–20.0
S.D. Mean	±2.63	±1.10	±2.13	±1.22	±2.45	±1.63	±2.36	±1.65
Red Cell Na								
Mean	19.8	21.6	19.8	20.7	19.4	20.4	19.7	22.4
Range	12.8–28.9	18.0–29.1	13.8–28.0	13.3–29.1	17.2–24.3	13.3–30.5	15.6–26.2	14.8–34.3
S.D. Mean	±3.8	±1.09	±3.4	±1.36	±3.9	±1.78	±2.7	±2.35
Red Cell K								
Mean	100.0	91.8	99.0	92.7	105.0	95.3	107.0	100.8
Range	83.0–112.0	80.2–99.7	91.0–107.0	85.3–100.0	96.0–117.0	84.6–105.2	100.0–115.0	85.9–106.0
S.D. Mean	±7.3	±2.48	±5.6	±0.94	±6.0	±2.56	±5.0	±2.46
Red Cell Cl								
Mean	65.0	Inadeq.	62.0	62.8	65.0	62.6	65.0	68.12
Range	60.0–72.0	data	57.0–72.0	52.4–74.0	56.0–72.0	50.7–69.9	53.0–76.0	60.3–76.9
S.D. Mean	±4.3		±4.1	±1.96	±5.2	±2.6	±7.2	±2.47
Hematocrit								
Mean	35.2	37.5	34.4	38.7	34.6	36.01	33.7	29.2
Range	30.2–40.4	26.2–47.7	30.8–39.1	29.6–52.0	30.7–41.0	29.3–42.3	30.6–38.2	25.7–37.0
S.D. Mean	±2.2	±2.18	±2.5	±1.36	±3.1	±1.53	±2.7	±1.65
Plasma Protein								
Mean	6.0	6.9	6.3	7.0	6.5	7.0	6.7	6.8
Range	5.1–6.9	6.3–8.4	5.7–7.0	5.9–8.2	5.7–7.3	5.7–7.8	6.3–7.0	6.2–7.5
S.D. Mean	±0.24	±0.35	±0.37	±0.174	±0.52	±0.29	±0.26	±0.20
NPN								
Mean	28.0	46.0	32.0	52.0	—	50.7	30.0	34.8
Range	27.0–29.0	29.0–64.0	25.0–41.0	34.0–90.0		32.0–77.0	28.0–32.0	31.0–39.0
S.D. Mean	±1.0	±2.45	±4.8	±6.74		±2.6	±1.5	±1.21

severity of the disease could be more closely correlated with the plasma bicarbonate level than with any of the other measured variables.

Erythrocyte Na was increased above the mean for normal children in each age group (table 2). There was no significant change in this erythrocyte ion when analyzed statistically with the critical ratios ranging from 0.2 to 1.76. This minor alteration within the erythrocyte does not parallel the changes for tissue cells calculated by others.[2] The

authors wish to re-emphasize that the erythrocyte sodium level of approximately 19 mEq./l. observed in normal children, which is the basis of comparison in this study (table 2), is higher than the level of 15 mEq./l. found in adults.[18] If a similar discrepancy exists between the tissue cells of infants and adults, the calculated percentage change reported by Darrow[7] may be high. Therefore one might speculate on the basis of these data obtained from erythrocytes that the movement of this ion from the extracellular into the intracellular compartment might be of less significance in the production of acidosis than postulated by others.[1] Unfortunately, data are not available on tissue cells of infants of various ages.

Similar to the calculations of Darrow[5,7] for tissue cells, the erythrocyte K showed a definite tendency to be decreased. In 89 to 100% of the infants in the different age groups the erythrocyte potassium level was below the mean for normal infants. In 14 to 55% of the cases the erythrocyte K was below the range for normal infants. There was no consistent relation between age and the degree of alteration in this ion, there being a close uniformity of the mean potassium level in all age groups. The critical ratios were observed to be insignificant. The directional alterations in this ion were similar to those observed for plasma Na, HCO_3 and Cl. Hallman and Kauhtio[20] studied thiocyanate space and plasma and erythrocyte concentrations of Na and K in 11 cases of infantile diarrhea in children 6 months of age or less. They observed plasma potassium levels ranging from 3.1 to 8.4 mEq./l. with an average of 5.5 mEq. Erythrocyte K ranged from 64 to 107 mEq./l. with an average of 92.7 mEq. The erythrocyte sodium concentrations reported by these authors are similar to those observed by the authors.

Erythrocyte Cl shows inconsistent changes as would be anticipated for the red cell. Alterations in the erythrocyte Cl due to the "chloride shift" conceivably may be associated with severe dehydration and acidosis; however, we do not believe that the "chloride shift" exerts any influence on the transfer of cations in and out of the erythrocyte.[19] This statement is further substantiated by the fact that arterial and venous differences in erythrocyte concentration of cations cannot be detected by present day analytical methods.

Hematocrit, NPN and plasma protein values which are included were increased in most instances with a significant increase in NPN in all groups, and a significant or near significant increase in plasma protein in the two younger age groups. As would be anticipated, it is clear that in the smaller infants in whom dehydration is most prone to develop there is an increasing tendency toward elevation of the NPN and plasma protein concentrations.

Discussion

These results which demonstrate that directional alterations occur in the electrolyte pattern within the erythrocyte as well as in the plasma of infants with diarrhea also demonstrate that these alterations are not always predictable in individual cases. The fact that there is no consistent inter-relationship between the alterations in plasma and erythrocyte cations in individual cases is illustrated in table 1. For example in A. B., B. H. and O. W. there was a severe acidosis with a normal erythrocyte Na and low erythrocyte K. The plasma Na was decreased and the plasma K remained normal. C. S., age 5 months, had a high erythrocyte Na of 29.1 mEq./l., a normal erythrocyte K, a severe acidosis, a low plasma Na of 122.6 mEq./l. and normal plasma K. G. H. demonstrated a picture similar to C. S. except for a low plasma and erythrocyte Na. Other inconsistent changes

can be observed in individual cases. The most consistent alterations were reductions in plasma HCO_3 and in erythrocyte K. In some instances however a low plasma HCO_3 was associated with a normal erythrocyte K.

The directional alterations referred to above are exemplified by the fact that the plasma Na, K, Cl and HCO_3 and the erythrocyte potassium levels tend to be depressed by diarrhea, whereas the erythrocyte Na tends to be slightly elevated. These alterations within the erythrocyte are similar to those reported for tissue cells.[5, 7] Also the change in erythrocyte K observed is similar to that reported by Lans, Stein and Meyer[21] in patients with a state of hypopotassemia due to a variety of causes. The present authors are prone to agree with these authors that "in dehydrated patients the erythrocyte potassium determination may be of value in the diagnosis of potassium deficiency." It appears therefore that the erythrocyte is a source of cells for flame photometric analysis from which useful information concerning alterations of K might be obtained.

The red cell has been vigorously criticized as a poor cell for measuring cellular changes compared to tissue cells, and perhaps justifiably so. It has been termed an "unstable" and a "dead" or "dying" cell, a cell without a nucleus, and a cell with a peculiar membrane which is permeable to Cl. However, in defense of the erythrocyte, one must consider the following: (1) its membrane must be an active one in order to permit such rapid interchange of O_2, CO_2 and Cl; (2) it is capable of maintaining differences between intra-erythrocyte and plasma ion concentrations which, with the exception of Cl, are similar to those recognized as being present and maintained between interstitial and tissue cell fluids; (3) the authors have observed (unpublished data) that the alterations which occur in the erythrocyte during diarrhea are reversible with treatment; (4) glycolysis occurs in the erythrocyte.

The authors have frequently used the information derived from the flamephotometric analyses of plasma and erythrocytes in obtaining a rough estimate of the body deficit of K.* The distribution of water is arbitrarily considered to be unaltered and the erythrocyte mass is ignored; nevertheless the estimate so obtained has been found clinically valuable as a guide in potassium replacement therapy.

Summary

By direct chemical and physical-chemical analyses, plasma and erythrocyte sodium, potassium and chloride concentrations, plasma calcium, bicarbonate and protein concentrations, and the blood NPN have been determined on infants between the ages of 2 and 15 months with severe diarrhea.

Considerable range and inconsistent changes serve to demonstrate that it is impossible to predict with certainty any definite relationship between the alterations in the various ions in individual cases.

A significant or near-significant reduction in the mean plasma Na occurred in infants with diarrhea under 11 months of age; the plasma K and Cl and the erythrocyte K definitely tend to be reduced, whereas the erythrocyte Na tends with few exceptions to show only a slight increase during diarrhea.

The plasma HCO_3 was always reduced and usually significantly so. The degree of

* Extracellular potassium deficit in mEq. = (normal plasma potassium concentration in mEq./l. —observed plasma potassium concentration in mEq./l.) × weight in kg. × 0.2. Intracellular potassium deficit in mEq. = (normal erythrocyte K in mEq./l. — observed erythrocyte potassium concentration in mEq./l.) × weight in kg. × 0.5. Total potassium deficit = intracellular + extracellular deficits.

acidosis and to a somewhat less extent the decrease in erythrocyte K were related to the severity of the diarrhea.

Significant increases in the blood NPN and plasma protein were usually observed.

The value of the erythrocyte as a practical medium for gauging intracellular ionic alterations which occur during diarrhea is discussed briefly.

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Spanish Abstract

Alteraciones en la Química Sanguínea Causadas por Diarrea en la Infancia Determinadas por el Análisis Directo del Plasma y Eritrocitos

Se determinaron por análisis químico directo y físico-químico las concentraciones de sodio, potasio, y cloro, tanto en el plasma como en los eritrocitos, y calcio, bicarbonato, y proteínas en plasma y nitrógeno no protéico en sangre, en un grupo de lactantes con diarrea severa cuyas edades oscilaron entre 2 y 15 meses.

Las oscilaciones considerables y la inconsistencia de los cambios demuestran que es imposible en casos individuales predecir con certeza correlación definitiva alguna entre las alteraciones de los distintos iones.

Una reducción de significación o casi significativa en el promedio del Na plasmático ocurrió en lactantes diarréicos de menos de 11 meses de edad; el K y Cl plasmáticos y el K de los eritrocitos mostraron en forma definitiva tendencia a reducirse, mientras que el Na de los eritrocitos tenía tendencia, con escasas excepciones, a mostrar un aumento ligero durante la diarrea.

El HCO_3 plasmático siempre estuvo reducido y generalmente en forma significativa. El grado de acidosis y en menor extensión, la disminución del K de los eritrocitos estaban en relación con la severidad de la diarrea.

Se observaron, en general, aumentos importantes en el nitrogeno no protéico sanguíneo y en las proteínas plasmáticas.

El valor del eritrocito como medio práctico para medir las alteraciones iónicas intracelulares que ocurren durante la diarrea es discutido brevemente por los autores.

University of Tennessee

Pediatrics

VOLUME 10 DECEMBER 1952 NUMBER 6

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

CENTRAL OFFICE—EVANSTON, ILL.

Condensed Statement* of Cash Receipts and Disbursements for Fiscal Year Ended June 30, 1952

Cash Balance, July 1, 1951		$133,089.42†
Cash Receipts:		
Dues	$78,219.48	
Initiation Fees	12,450.00	
PEDIATRICS	98,170.03	
Meetings—Annual and Areal	77,592.71	
Pamphlets	2,416.79	
Interest	2,110.17	
Grants	26,383.70	
Total Cash Receipts		297,342.88
Total Cash Receipts and Beginning Balance		$430,432.30
Cash Disbursements:		
Meeting Expenses—Annual and Areal	$44,000.23	
Committee Expenses	14,131.08	
Editorial Office	11,926.82	
Executive Board	9,273.62	
Office Equipment	3,637.01	
Postage, Stationery, Printing and Office Supplies	7,091.06	
Pamphlets	3,130.78	
PEDIATRICS—Advances for Publishing Expenses	28,407.50	
President's and Vice-President's Expenses	1,107.78	
Rent and Light	7,561.06	
Salaries	41,975.07	
State and District Chairmen's Expenses	733.86	
Telephone and Telegraph	599.88	
Travel—Executive Secretary	2,699.83	

* The complete audit report is available to any member of the Academy at the Central Office, 610 Church St., Evanston, Ill.

† NOTE: Includes restricted grants, special reserves and Central Office working funds.

Montevideo Expenses—Drs. Grulee and Gomez	3,834.25	
Retirement Plan Annuity—Dr. C. G. Grulee	50,045.00	
Grulee Award	734.15	
Retirement Plan Insurance—Employees	5,482.88	
M & R Latin American Scholarship	1,500.00	
Sundry Expenses	3,579.91	
Refund to National Federation for Infantile Paralysis, Inc.	4,358.67	
Securities Purchased—Cost	49,796.88	
Total Cash Disbursements		295,607.32
Cash Balance, June 30, 1952		$134,824.98†

ACCOUNTANTS' CERTIFICATE

We have examined the books of account and records of the American Academy of Pediatrics, Central Office, for the fiscal year ended June 30, 1952 and, as a result thereof, we hereby certify that the above statement of cash receipts and disbursements correctly presents the cash balance of the Central Office of the Academy at June 30, 1952 and its cash transactions for the fiscal year ended on that date.

E. J. WIEDMAN & COMPANY
Certified Public Accountants

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Dr. Elmer Walter Barron
R.F.D.
Rockland, Mass.
Died Jan. 1952

Dr. Robert Blessing
2608 Alamanda Court
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Died Oct. 29, 1952—EMERITUS

Dr. Malvin Finkelstein
2139 Hudson Blvd.
Jersey City, N.J.
Died June 20, 1951

Dr. Rockwell M. Kempton
333 S. Jefferson Ave.
Saginaw, Mich.
Died April 5, 1952

Dr. Jaime Ramirez Acha
Casilla No. 272
La Paz, Bolivia
Died Jan. 1950

Dr. Louis Charles Rosenberg
11 Murray St.
Newark, N.J.
Died Nov. 3, 1951

Dr. Eugene H. Smith
714 Eccles Bldg.
Ogden, Utah
Died March 29, 1952

Dr. LeRoy T. Stokes
95 Summer St.
Harverhill, Mass.
Died June 11, 1952

Dr. Joseph S. Wall
3314 Porter
Washington 8, D.C.
Died Sept. 17, 1952—EMERITUS

Dr. James J. York
930 State St.
Schenectady, N.Y.
Died June 4, 1952

Round Table Discussion

PEDIATRIC DERMATOLOGY

EARL D. OSBORNE, M.D., Buffalo, N.Y., *Chairman;* JOHN R. ROSS, M.D., Toronto;
NORMAN M. WRONG, M.D., Toronto
WALTER C. MCKEE, M.D., Chicago; GEORGE S. FRAUENBERGER, M.D.,
Evanston, Ill., *Secretaries*

Chairman Osborne: The material which we will cover will be material which must be spoken about in terms of groups of people, types of individuals and different classifications of diagnosis. We will lose a great deal of the effect of what we have to discuss if we get off on a small subject connected with an individual case, so I hope we can refrain from citing specific cases. You all recognize that we can't make progress if any of us are going to present specific individual problems on a specific case.

Fortunately we have some disagreement among members of the panel for where everyone agrees there is a lack of interest, especially in the field of cutaneous diseases, and particularly in the eczematous diseases. If we seem to disagree it is because the material calls for disagreement and the literature backs us up on that disagreement.

We are going to start with the general phase of the subject: the care of the skin of the newborn. I am going to ask Dr. Norman Ross to discuss the care of the skin of the newborn from the standpoint of the pediatrician.

Dr. Ross: In these newborn infants overzealous cleaning of the baby and too much anxiety on the part of the nurse following birth is apt to do far more harm than good. The baby when born has a membranous covering that should not be too thoroughly and vigorously removed. Soap is not advisable. Plain water will remove sufficient of it and, in fact, delay of thorough bathing of the infant for a few days would probably be advisable. As to applying any antibacterial preparation to the skin—this can be done if you are finding there are a number of cases of infection in the hospital at that time. But even at this we don't use it often and it probably is not advisable.

Chairman Osborne: Dr. Wrong, would you please discuss this from the viewpoint of the dermatologist and include in that what is known from a bacteriologic standpoint regarding the presence of pathogenic organisms on the skin of newborn and young infants.

Dr. Wrong: I feel very definitely that this is something that concerns the pediatrician much more than the dermatologist. After all, it is the care of the normal skin and the pediatrician, the obstetrician or the general practitioner is the man who sees the child within the first few days, weeks or months of life. The dermatologist only sees that child when it develops something abnormal with the skin, so that I feel that the question of care is one which pediatricians can discuss much better than dermatologists. As far as the bacteriology is concerned Dr. Osborne suggested that I look this up and I was amazed how little there is in the literature, that is, on the subject of the bacteriology of the skin of the newborn.

The bacteriologist in the hospital looked it up also and neither of us could find much. Dr. Osborne told me that they had found that up to 4 or 5 days the skin of the newborn infant is remarkably sterile and that the organisms begin to appear after that.

Chairman Osborne: I want to add a word along this line. Most of us know that at least in the private hospital the obstetricians control the first few days or weeks of life of many infants. In other institutions the infants are turned over to pediatricians. This is especially true in the free institutions. There are a number of institutions that have instituted a new regime of leaving the vernix on for a period of from 2 to 5 days, then gently removing this material with lukewarm water and no use of soap whatever. For a period of at least the hospital stay and for 3 or 4 weeks

Presented at the Annual Meeting of the American Academy of Pediatrics, Toronto, Oct. 23 and 24, 1951.

at home no soap should touch the baby's skin. When soap is used later it should be a superfatted soap.

However, we must remember that any soap by definition is an alkali. No soap, no matter how good, has a pH of less than 9. Alkali has a marked effect on a newborn baby's skin where the horny layer is exceedingly thin. The epidermal cells are exposed to the action of alkali and alkali is of and by itself a sensitizer. Many skins become hypersensitive later to any alkali. They become particularly sensitive to the O-H group and for that reason alkali should not be used on young skin. When soap is used it should be superfatted soap and then the child should be bathed not more than 3 times a week. If a further bathing is necessary, the groin, the thighs, the feet, etc., those parts can be rinsed off with plain water or oatmeal water or starch water of any kind without the use of soap. We want to emphasize that the use of soap in the early weeks of life should be stopped.

I would like to ask Dr. Wrong to discuss the use of oils applied to the surface of the newborn skin during the first few weeks of life.

Dr. Wrong: I think that oils coat the skin and seal off the glands in that way. If there are organisms in the area there is more tendency for them to invade the oil and sweat glands. Oils which contain perfume and various antiseptics may act as a sensitizer and produce an eruption. The tendency in the past, maybe due to overzealous advertising, has been to overdo the use of skin oils and we have all been led to believe (if we read the ads) that no harm can come from applying baby oil. I think quite a bit of harm can come from baby oils. As Dr. Osborne has said, the baby's skin is better if it is cleaned with plain water and if soap is used sparingly; certainly the skin should not be covered with grease or oil which may contain some perfume or substance which will in itself be a sensitizer.

Chairman Osborne: It is true, also, Dr. Wrong, that some oils, with no preservative added, will in themselves leave a fertile medium for the growth of bacteria.

Dr. Wrong: We have been told that some of them are excellent culture mediums.

Chairman Osborne: Dr. Ross, what do you think of the action of oils and greases on the young infant's skin in precipitating miliaria?

Dr. Ross: I certainly believe that a lot of these infants tend to show miliaria more readily if their skin is oiled or greased. Their skin should be dry and the pores should be open in order to counteract the excess heat that the mother exposes them to through overdressing.

Chairman Osborne: Your problem of excess heat brings up an interesting point: I think the average baby that I see in my office has about 5 times too many clothes on. Particularly the first baby who comes in accompanied by the mother and father. They unwrap about 4 layers of blankets, then the child is in another layer of woolen. The child is sweating profusely and may or may not have an eruption.

I would absolutely forbid the use of any oil, simple oil, olive oil or any of the patented makes in the scalp.

One important phase in the care of the newborn in my experience is this; in hospitals, especially, and in many private homes, newborn babies are, as Dr. Wrong pointed out, exposed to excessive heat. I am often called in as a consultant where the pediatrician has made a diagnosis of impetigo involving the groin with the formation of clear vesicles and seldom see any pustules until later.

The thing I want to point out is that it is a miliaria. It is not impetigo and is not due to any faulty care of the child in the hospital. There have been a lot of law suits over the presumed faulty care of the newborn infant in the hospital nurseries. It is almost always a miliaria if, when organisms become present, a pustular eruption can be produced which takes weeks and weeks to clear after it is once developed.

The next subject we want to take up is the prophylaxis of impetigo contagiosa. This has been a live topic for quite a number of years—less so at the present time, fortunately. We recognize that all sorts of antiseptic preparations have been used in years gone by. Ammoniated mercury was one of the first. In various strengths—3% ammoniated mercury seemed to be optimal, although 5% was used in some. Then sulfa drugs were used as prophylaxis against impetigo. Then penicillin ointment and now more recently other preparations have been used as prophylactic agents against impetigo contagiosa. I would like to state now that, in our opinion, the best prophylactic agent which is harmless and does not sensitize, is a water solution of either aureomycin or neomycin. You may put a 50 mg. tablet in anywhere from 2 up to 8 ounces of water and sponge it on. It is an excel-

lent prophylaxis if a prophylaxis must be used. Many of the hospitals find it unnecessary to use it today if the directions we have already given are followed. It isn't necessary to use prophylaxis against impetigo.

The water solution is nonsensitizing whereas the ointment forms are sensitizing.

Dr. Wrong: I am interested in what Dr. Osborne has said regarding the use of aureomycin and neomycin.

Chairman Osborne: This preparation can be used if there is impetigo in the nursery by sponging on all the infants about 3 times a day.

Dr. Wrong: We have heard a lot about lotions containing G-11 used to sponge the infants. The pH is around 7 and I am told by some of my pediatric friends who have used it in the nursery that it has seemed to cut down the incidence of impetigo. These are to be used only if the child has been or may have been exposed to infection.

Dr. Ross: A good many of my colleagues and I have used sulfa ointment and we haven't found sensitizing effects very often. I think the reason is we prescribe it for only a 4 or 5 day interval, not for a week or 2 weeks. It works remarkably rapidly and seems to clear them in 2 to 4 days at the most. I know if these ointments are kept up for a period of weeks you may get sensitizing effect.

Question: What do you mean by sensitizing—in the sense of allergy or just what?

Chairman Osborne: I mean in the sense of developing a specific hypersensitivity to aureomycin. We have not had one single case of specific hypersensitivity to water aureomycin. In many hundreds of cases this has not happened.

There are quite a number of cases in our experience of hypersensitivity to aureomycin ointment. I want to point out that in all those that have been investigated, it is believed the sensitization has been due to the base and not to aureomycin.

Dr. Albert J. Sheldon, Santa Ana, Calif.: What about the use of talcum or antiseptic talcum powder in the prophylaxis of impetigo?

Chairman Osborne: Plain talcum is not sufficient to act as a prophylaxis against impetigo contagiosa.

Dr. Sheldon: Do you have the objection to talcum that you have to oil in the routine care of the newborn?

Chairman Osborne: Not at all. Talcum does not plug the sweat pores.

I would say on the basis of my experience that aureomycin and neomycin as I have outlined are the most effective and the least sensitizing and that last is an important thing. We found in a survey of 200 cases of eczema in children under the age of one month that in 20% of them the original dermatitis or eczema was induced originally by sensitization to ammoniated mercury. This was a survey made about 15 years ago. It shows the very real point that initial sensitization in an individual constitutionally tending toward sensitization or allergy that an allergenic drug like ammoniated mercury can start the individual off on a train of allergenic reactions. So I would urge the use of a nonallergenic substance like the water solution of aureomycin or neomycin and there may be newer ones coming along in the near future that will be even better.

Inasmuch as we are discussing infections of the skin we will include not only the newborn but all the other age groups of infants coming under the guidance of pediatricians. I would like to have Dr. Wrong discuss in general at this time the treatment of bacterial infections of the skin, particularly from the standpoint of evaluation of bactericidal agents.

Dr. Wrong: In the treatment of any bacterial infection of the skin and certainly if you want to be scientific at all it is essential that this be controlled by bacteriologic sudies; if at all possible in your practice, do cultures. You will gain a great deal of interesting information from the skin culture—pustules, skin crusts, etc. Are you dealing chiefly with staphylococcus or streptococcus hemolyticus or with a combination of both? That is important as a start, and then in the general treatment of pyogenic infections of the skin, I think, probably today the antibiotics which we have available are the best treatment we have. Certainly in the old days of ammoniated mercury we saw nothing like the spectacular results of treatment that we see today with the antibiotics. As far as the antibiotics are concerned, I prefer to use the ones which we are not going to use by injection or orally. Bacitracin is one which has a high index against both staphylococcus and streptococcus. One in particular on which we are doing some work is neomycin. This is particularly effective

against staphylococcus, not as effective against streptococcus, but interesting enough it is very effective against Pseudomonas aerogenes, which may be of real value.

I think we should bear that in mind as a general principal. Let us use substances on the skin which at least in the laboratory have a high killing index against bacteria and have a low sensitizing power against the skin. They are not liable to produce a dermatitis.

Chairman Osborne: Dr. Ross, would you discuss for us the use of these substances on the skin and the important time intervals from the standpoint of sensitization. Explain to the group why it is you can use sensitizing drugs for 1 or 2 days where you can't use them for 14 days or more. Also, what do you favor in the cure of skin infections?

Dr. Ross: When using sulfa ointments it takes a period of time to build up a sensitivity to that particular drug if the child seems to develop that sensitivity. It takes 10 days to 2 weeks in animal experimentation to sensitize animals and the same occurs in these infants.

Chairman Osborne: I would like to summarize what I feel about any antiseptics used on the skin for any infection—that includes impetigo contagiosa, pediculosis, the pustule element in ordinary miliaria, a spreading pustular infection around a source of injury such as an insect bite and all other skin infections. Dr. Ross has rightly pointed out that to sensitize an individual you must use a preparation about 14 days or longer. Many men, not only pediatricians, but dermatologists and general practitioners prescribe a sulfa drug or a penicillin ointment and never put any time limitation on its use. The same goes for ammoniated mercury, sulphur ointments and many other things. If you are going to use a sulfa drug on the skin you must put on a time limit, usually 3 or 4 days. If you are going to use penicillin preparations you must put on a time limit or you are going to sensitize. Now the sensitizing index of sulfa drugs on the skin in ointment form has been found to be in a large group of cases about 30% if the drug is used on more than 2 weeks, about 20% in penicillin if used more than 2 weeks. For that reason I must disagree with my colleague, Dr. Ross. He uses the sulfa drug because he limits the time but I don't think in the view of our present antibiotics that there is any indication whatever for the use of any sulfa drug or any penicillin on the skin. They should only be used when they are life-saving in serious infections such as pneumonia or appendicitis, as long as we have the new antibiotics that can be used more easily or cheaply and without any risk of sensitization.

Dr. Wrong has pointed out that neomycin is coming on the market and is already on the market in certain parts of the United States. Men are having difficulty in getting it. It is the best antibiotic we have at the present time. Sometime ago I heard about penicillin 98. It is not yet on the market but it is still better than any of the others, so that we are in for a period of improved antibiotics that have a wide effect on bacteria and which will become increasingly important in the care of the skin in the future.

Dr. Irving Weinstock, Brooklyn: For the treatment of impetigo contagiosa, was the treatment with injection of penicillin purposely left out?

Chairman Osborne: That was purposely left out. The treatment of impetigo should consist of the liberal use of soap and water twice a day and the use of one of these antibiotics. Personally I favor aureomycin or neomycin.

Comment: In an extensive impetigo, in addition to using one of the antibiotics locally I would also give penicillin intramuscularly.

Chairman Osborne: I hadn't thought about that but I would agree with that too. Where there is any possibility of blood stream infection there is no reason why you shouldn't use penicillin by injection.

Dr. Frank E. Roth, Hartford, Conn.: Do I understand that you prefer at all times to use aqueous solutions of these antibiotics?

Chairman Osborne: That is correct as far as I am concerned. I think I am the only one of the panel who has had experience with them. You can try them and make up your own mind. I am telling you my own experience.

Dr. Wrong: I have used aqueous solutions of neomycin in external otitis and I agree with Dr. Osborne that it seemed to be of great value.

Chairman Osborne: We want to cover the subject of external otitis in some detail for you here because you get plenty of those cases in pediatric practice. Most of them result from extension of the seborrhoid process down from the scalp. Too many cases of otitis have been treated as fungus

infections. You can find the same organisms on normal skins. They are seldom pathogenic; they are staph, strep, hemolytic staph and strep. The medium present in those areas, because of the specialized oil glands, is highly favorable for the growth of certain bacteria. I would like to ask Dr. Ross to discuss the treatment for external otitis of the seborrhoic variety.

Dr. Ross: I do feel that in these cases of external otitis if one cannot visualize the ear drum, if there is a great deal of debris, considerable benefit may be derived from irrigation in cleaning up the debris to be sure you are not dealing with otitis media. Then I always take cultures and I agree with Dr. Osborne that a lot is usually found there. George Lewis of New York, among others, has proved pretty conclusively that the so-called fungi that are found in the ear are rarely pathogenic.

Locally we have been using aqueous solutions of neomycin and of bacitracin and we have also been using neomycin in ointment. It is also important in external otitis to clean up the scalp; many of these cases are associated with a great deal of dandruff and that certainly is a factor in continuation of their disease.

Chairman Osborne: I would like to discuss this subject a little longer. As Dr. Wrong intimated bacillus pyocyaneus is almost certainly the organism at fault in the prolonged chronic cases. However, you always find positive cultures of pathogenic streptococcus and straphylococcus. You find the others, too, but they are unimportant. Now, how best to treat this combination of organisms? There is one remedy that has been used for a great many years but that has been forgotten by a great many physicians. That is acetic acid. Up until the use of neomycin, as Dr. Wrong pointed out, acetic acid is still the best remedy against the bacillus procyaneus. Many men in general practice have used vinegarin one to 4 or 5 parts of water in treatment of the external type of otitis. Now for a period of 3 years we have been using irrigations of the external auditory canal with a solution in which the active ingredient is acetic acid. You purchase an ordinary ear syringe, irrigate the external ear canal with dilute Burow's solution of 1:20 or if tablets or powder of Domebaro solution are preferred you use one powder in a pint of water. It will keep in a mason jar. Irrigate the ear 3 times a day with that solution and then 3 times a day irrigate the ear with water solution of aureomycin or neomycin.

Question: What percentage of neomycin has Dr. Wrong been using?

Dr. Wrong: My recollection is 50 mg. in 10 cc. of water.

Chairman Osborne: So far we have not used neomycin because it has not been generally available. We have had to use aureomycin. I think we should wait until neomycin is generally available.

Chairman Osborne: We have been talking about the seborrhoic type of external otitis where the seborrhoic dermatitis of the scalp often begins as a cradle cap. Sometimes the children develop a so-called type of seborrhoic eczema. You must treat the middle ear infection before you can hope to clear up the infectious dermatitis that develops in the external ear and down the neck from the drainage.

Dr. Lawrence Breslow, Chicago: Would you please express your opinion on vioform cream? A lot of us use it for these cracks when there is no other seborrhea.

Chairman Osborne: It is an excellent preparation for these chronic cracks which are not associated with seborrhea dermatitis. In children it is best to use below 3%, preferably 1 or 2%.

Dr. Margaret A. Limper, Louisville: Is there any objection to using peroxide irrigation to get rid of the excess debris in the external canal before starting treatment?

Chairman Osborne: There is no objection to that at all; I merely emphasized that we should not use grease and oil or salves in the ear canal. It plugs them up; it very often shuts them off with the growth of bacteria inside of the plug. Use of water solution, either vinegar or aureomycin, to irrigate out is best.

Dr. Warren Fargo, Cleveland: Dr. Wrong speaks about clearing up the scalp. By implication does he mean that neomycin will do that?

Chairman Osborne: We will discuss that at length a little later on.

Dr. Frank E. Roth, Hartford, Conn.: You speak of cracks in the ears where you have seborrhea but how about treating the crack in the ear where you have no seborrhea? What is that caused from?

Chairman Osborne: That is often due to staphylococcus or streptococcus, usually the latter. As a matter of fact, cracking behind the ear is more commonly associated with seborrhoid dermatitis than with any other condition. And you find those same organisms in seborrhoic dermatitis. Now let us not confuse the development of specific allergy to nickel from the bows in glasses. That is

a different condition when it begins at the top of the ear; bacteria always grow in that. We are talking now about the cracking in the fold of the ear and the formation of seborrhoic or yellowish crusts which extend down on beyond the lobe of the ear. I agree with Dr. Wrong and prescribe 3% vioform cream or less depending on the age of the child.

Now about the scalp: there are hundreds of preparations which may be used on the scalp. Here is a preparation that is clean and does not contain any grease: depending on the age of the child, anywhere between 2 to 5% salicylic acid, one tenth of 1% mercury bichloride, propylene glycol 30% in 95% alcohol. Then there is a commercial preparation called topisol® which can be used instead of propylene glycol. It is a clear nongreasy lotion that can be applied every day, it dries readily and is very potent. You can alternate that with a water solution of aureomycin or neomycin. Both have the great value of not staining the hair and both are water soluble. They can be sponged in once a day where there is discharge and evidence of bacteriologic staphylococci and streptococci. If you have time to do that, the aureomycin and neomycin are extremely effective in those cases.

That also applies to the condition when it appears in the eyebrows: granulated eyelids are evidence of seborrhoid dermatitis; the same organisms are present there. Aureomycin, terramycin and neomycin in the treatment of the eyelids is much better than yellow mercury of oxide.

Question: Is your preparation used in the scalp just once a day?

Chairman Osborne: Once a day is sufficient. I would like to bring up one other point at this time. I have had opportunity to observe quite a number of cases with the development of dermatitis, some mild and some very severe, from the use of sulfa drugs and penicillin in the mouth and nasal cavities. As far as I am concerned I am opposed to the use of sulfa drugs and penicillin in the mouth or in any cavities. I am in favor of the water solution of aureomycin or neomycin or terramycin as a mouth wash or a gargle.

Dr. Ross: I agree with Dr. Osborne that you get greater absorption from the mucous membrane and I never prescribe any kind of sulfa ointment to be used in the eye or nose.

Dr. Wrong: I believe that one of the most prominent places where we see the development of a dermatitis due to medication is in the external ear where sulfa has been used a great deal in the past and because there is resistant infection there, penicillin ointment is of no or very little value. It is common to see a contact dermatitis due to medication about the external ear.

Dr. Alonzo deG. Smith, Washington, D.C.: Did I understand you to say that you oppose the use of sulfa or penicillin in the nose?

Chairman Osborne: I do. I feel that there are other things that you can use without any danger that are just as good or better.

While we are talking about skin infections we want to talk about parasitic skin infections, scabies and pediculosis—pediculosis capitis and pubis particularly. We will not go into the diagnosis of these conditions but we do have a few words to say regarding treatment of these conditions, especially in children.

Dr. Wrong: When I came back from the services, I was entirely sold on the use of benzyl benzoate, 20% emulsion in scabies. It works extremely well in adults but it does not work as well in children because it causes a lot of stinging and burning and, therefore, the parent does not apply it. For that reason I have gone back to the use of sulphur ointment, which we use in 10% or in the case of a very fair thin-skinned child 7½%, applied for 3 nights. It is mussy; children don't mind it but adults do. However, if applied properly for 3 nights covering every square inch of body from the chin to the toes, it is effective.

As far as the treatment for pediculosis is concerned we have used a 5 or 10% DDT in talcum powder, not in solution, applied once or at the most twice a week for 2 applications. It is very effective. It does not remove nits, however, which is a handicap, particularly in a small girl with pediculosis capitis; the fond mother does not like to see the nits remaining in the hair.

Dr. Ross: I use sulphur ointment in the prescribed strength with good results.

Chairman Osborne: I have fairly strenuous feelings about the treatment of scabies in children as well as adults and I agree with Dr. Wrong and Dr. Ross in regard to the sensitizing benzyl benzoate in strengths of 20 or 25%, the ordinary emulsion. It simply will not work in children. If you are going to use this per cent you are going to get a lot of children with sensitization from its use. Especially if the treatment is repeated. There is a very excellent preparation on the market. It combines an all-purpose parasiticide with an analgesic that is an excellent preparation. It can be

used not only on scabies but in pediculosis capitis, pediculosis pubis. I mention a product which is on the market which contains only 10 per cent benzyl benzoate which is well within the non-irritating range on children's skin. It contains 1% DDT, 2% benzocaine, 2% of an emulsifying agent. It is known as topocide® and is put out by Lilly. The directions for its use: a full bath with soap and water—all the pustules open, the crusts and scales removed. This preparation is then sponged on with a little cotton or gauze from shoulders to toes without missing a single square centimeter of body surface. The first layer will dry in about 5 or 10 minutes and then another layer is sponged on from shoulders to toes. The child or adult is put to bed in a warm bed for a period of 8 hours, overnight at least; they then take a bath with clear water and use plain talcum or calamine lotion. This treatment under no circumstances should be repeated in children under 4 weeks.

In children you will find the development of many pustules due to killing organisms in the skin. You will have abscesses and a spreading dermatitis. In many cases some of them are deep; they do not respond. These cases immediately after they are treated for scabies must be treated for their infectious dermatitis, as a result of secondary infection; those can be treated with a water solution of aureomycin, terramycin, neomycin; they can be treated with moist dressing. One of the greatest mistakes of men in general practice is the repetition of that treatment if the patient does not get well in a week. In a bad case of scabies in an infant, the itching may be relieved the first night with this application but very often at the end of a week the child's skin looks worse than it does the first night. The reason for that is that tremendous numbers of organisms are killed and the eggs killed by the preparation itself. A secondary infection sets in and a rough time is had by all until a week or 10 days or until the secondary infection can be brought under control.

We insist that every member of the family be treated, whether the other members of the family show evidences of scabies or not.

In the case of pediculosis capitis, wash thoroughly with soap and water, dry the scalp, apply this preparation thoroughly and put on some form of a cap overnight and wash out thoroughly with soap and water. One treatment is usually sufficient and certainly one treatment is all that is necessary in pediculosis pubis. The benzocaine relieves itching and since you only apply it once it has no sensitizing value.

Question: Have you had any experience with a product on the market for the treatment of scabies called quell®, which is a water-soluble cream? It is supposedly nonsensitizing.

Chairman Osborne: We have had quite a little experience with it and found it was not superior to benzolbenzoate.

I would like to ask Dr. Wrong to start the discussion on flea bites. Fleas are no respecter of persons. They do pick out certain individuals who probably become sensitive to the substance which the flea injects. Fleas get on the feet and legs from the floor and garden; certain cat and dog fleas will attack the human as well as the common sand or garden flea.

Dr. Wrong: DDT is remarkably effective in killing fleas. Calamine lotion containing one fourth per cent methol and one per cent phenol is very effective. The important thing is the eradication of the fleas. The other thing is to be flea-conscious. If you see a child with an eruption, think of the possibility of flea bites—particularly if the lesions seem to be about the ankles and later involve the legs, thighs, etc.

Chairman Osborne: Flea bites are becoming more common in the East. The men in California now have been familiar with flea bites for a number of years but apparently the incidence of flea bites is rapidly on the increase in the East. We are learning a great deal about fleas. For one thing, only about one person in 20 or 30 is susceptible or, in other words, develops a specific allergy to the venom of the flea. This explains the low incidence in families. Most adults, when you make a diagnosis of flea bites, doubt it. The best way to get around that is to tell the parent of a child that you have had flea bites too. There is nothing wrong about it.

We also know that there are ground fleas. They are everywhere on the ground. All animals get fleas and they are carried around. You can get flea bites on the golf course as I myself do. They remain viable in carpets, rugs and furniture for months which explains why under the proper conditions the eggs hatch and produce fleas that will bite. One of the common sources of infection is cars in which dogs ride and have deposited eggs on the seat.

Dr. Ross: We do use the antihistaminics in bee sting, where a person is particularly allergic

to the sting; the antihistaminics do give fairly prompt relief in most cases. I haven't had much experience with the flea bite.

Chairman Osborne: Well, you agree, Dr. Ross, that any antihistaminic should help any insect bite, that is, theoretically?

Dr. Ross: Yes.

Dr. Frank H. Douglass, Seattle: Is that used locally or orally?

Dr. Ross: Both; I usually give the tablets and apply the ointment as well. They get a more prompt relief from the locally applied ointment and then the tablet will tend to reduce the swelling.

Chairman Osborne: It should be by mouth and as Dr. Ross has pointed out there is an analgesic effect from antihistaminics which is aside from its antihistamine effect. They are all mild analgesics and for that reason they sometimes relieve itching locally. They are sensitizers too, but they can be used locally with benefit as Dr. Ross has said.

Now there are one or two more things about insect bites that are of practical importance to all of you. One is this: the use of the army insect repellant made by DuPont and used by all the allied armies in the war. #618 is an excellent insect repellant and can be sprayed on or sponged on the skin or on clothing. Furthermore for many insects including fleas but not including most flies, especially the black flies of Canada, vitamin B^1 taken internally is an insect repellant. In children up to a weight of about 85 or 90 lbs. the dose is 25 mg. to 50 mg. 3 times a day. It doesn't always work but I have had some startling and phenomenal results in prophylaxis by the use of thiamin-hydrochloride by mouth, combined with the insect repellant sprayed on.

Chairman Osborne: I would suggest in severe cases where the patient is in bad shape from multiple bites that you use intravenous antihistaminics. With children you can gauge your dose from 5 up to 30 mg. daily intravenously, sometimes given twice a day.

Dr. Ross: I forgot to mention ACTH. I think that would be the ideal method of rapid treatment.

Chairman Osborne: I would like to point out before we go further that the panel has agreed on this: that wherever the allergen is removed, ACTH is extremely effective treatment.

I would like to discuss the subject of hemangioma in some detail. I realize that some pediatricians advise against any treatment at all of hemangiomas. But that is more easily said than done. If the hemangioma is on the trunk or any nonexposed part, I often advise that it be left alone, because spontaneous thrombosis is bound to occur sooner or later and the lesions disappear with only some faint atrophy remaining. A large number of hemangiomas are unsightly. They occur on areas that embarrass the parents and create a terrific sense of inferiority on the part of the child; furthermore many of them undergo spontaneous ulceration, especially those subjected to moisture. All the things you don't want to happen can be avoided by careful treatment. Now let it be said that no member of this panel is advocating the widespread treatment of hemangiomas by persons who are not qualified trained individuals. I would be the first one to admit that thousands have been treated injudiciously in years gone by, that scars have been produced and all sorts of ill-considered treatment has been given that has only resulted in criticism of the medical profession.

Properly given, treatment can be rendered to these hemangiomas that is extremely satisfactory. The treatment is rather simple today and must be with highly filtered radiation. We don't want to go into details of technic but that is the secret of it. A minimum of 1 mm. of lead filtration must be used and not over ⅔ of an erythema dose must be given. The treatment must not be repeated under 2 months and in subsequent treatment the interval should be 3 months. Now you can treat a hemangioma the size of a dollar in the scalp or a half dollar or less can be treated with radiation in that way without the loss of any hair. You can't tell where the lesion was.

Whenever you see a hemangioma treated and there is radiation reaction you can make up your mind that the result a year or 2 or 3 later is going to be poor. You must never get reaction from radiation.

Now we want to say a few words about pigmented nevi. It must be remembered that hairy nevi never or almost never become malignant. However, both flat and raised pigmented nevi of any color may become malignant. A raised pigmented mole is no more harmful, per se, than is a flat pigmented mole. The final differentiation should be on the basis of geographic distribution on the body and whether that particular area is subjected to irritation. If a pigmented nevus, either flat or raised and nonhairy, is subjected to irritation, it should be removed. They are best removed by plastic surgery. When they are small they can be removed by a man experienced in electrosurgery.

The areas most subject to irritation are the feet, toes, around the ankles, the palms, fingers, face or where there is a belt, girdle or strap or article of clothing which produces frequent trauma. Those lesions should be removed. However, it is impossible to remove or recommend the removal of all pigmented nevi. Our basis for differentiation should be on the basis of whether the lesion is subject to irritation.

Dr. Wrong: I would also like to point out that on an average we have 15 to 20 of these pigmented nevi and malignant melanoma is a relatively rare disease. When a mother consults us about a child who has a nonhairy mole and asks about the chance of this becoming a malignant growth, I think we can say it is extremely remote. I agree with Dr. Osborne that these lesions in irritating areas should be removed but the chances of one mole becoming malignant is extremely less than that child being struck by lightning.

Question: What about the fact that you may cause it to become malignant by removing it and along with that what about the time interval for removal? There has been some question as to whether they are better removed before puberty or after puberty.

Chairman Osborne: It is perfectly true and should be emphasized that pigmented moles in children do not reach their greatest development until sometime around puberty. Therefore, if a pigmented mole is removed too early, the surgeon, unless he goes over a very wide area, is not going to get it all. I seldom remove any of these pigmented lesions (unless they are irritated) until a child is around 10 or 12 years of age. Furthermore regarding whether removing these lesions induces malignancy—if it is improper treatment with acid or if it is due to injudicious electrolysis treatment, it is bad treatment. It must be total removal and you must make sure that you get all the pigment cells. If it is surgical removal by a plastic surgeon I always take an indelible pencil and make an oval mark along the lesion from ⅛ to ¼ inch beyond the border of the lesion where the excision should be.

Dr. Wrong: Regarding radiation of moles, I think it is extremely poor treatment. We have all seen cases where heavy doses of radium have been given which have resulted in radiation changes in the skin and a mole growing in the center of this radiation change.

Chairman Osborne: We will now discuss the cutaneous allergic conditions in children. This is a big subject and we are going to take it up in detail and follow a definite outline.

We will catalogue these conditions in children chronologically depending on the age of the child. A dermatitis in a newborn infant is different from a dermatitis in a child 5 or 10 years of age. That there are several age groups as a factor is something we all agree on. When you speak of percentages as applied to the various types of eczema occurring in infants and children, it depends entirely on the age group in which the child falls. Certain causes are operative in the newborn that do not operate after 6 months. Certain causes are operative in the period of from 3 to 5 months that are not operative after 5 years so that we are going to talk about this from a chronologic standpoint. Secondly, and from a general standpoint, it is well to remember that external contact, when a contact dermatitis is produced by an allergen, is produced by reaction in the epidermis and the essential lesion is a vesicle in the epidermis. That comes from the application of any chemical substance. Poison ivy is a good example.

Dr. Ross: In the young infants, as we mentioned before, caution is necessary in the use of soaps. In some young infants they definitely act as irritants. The overvigorous use of soap is to be avoided.

Another cause of trouble is the use of oil and particularly medicated oil. These block the pores of the skin and are a possible source of irritation. Some of the drug houses stress the use of these oils so much that the mothers frequently overdo the use of them.

Chairman Osborne: I would now like to have Dr. Ross discuss contact dermatitis in the young age group. Remember we are now talking about babies and young infants.

Dr. Ross: Dermatitis venenata is a contact dermatitis and here comes into play the fact that wool may act as a primary irritant and also as a sensitizing agent. Babies in the northern climate are in contact with wool all winter long and, though we tell the mother to avoid the use of wool, we find them putting a wool blanket right up to the baby's face and the baby is breathing in the wool lint.

Chairman Osborne: Dr. Ross, how old does a child have to become to show the first effects of sensitization?

Dr. Ross: There is an interval, in my experience, of 3 to 4 weeks before you get a true dermatitis

—allergic types of dermatitis occurring. From then on you must be on the lookout for these cases. I believe that food plays a large part in this age group. I find out exactly what foods the baby has had from birth and if the baby is on breast milk. I believe the irritation may be due to the breast milk containing an allergen. If the baby is on cow's milk plus orange juice and cod liver oil, it may be one or all 3 of these foods which have some effect on the allergic dermatitis. I like to give evaporated milk; this milk should be boiled a little longer than usual. I am in the habit of telling them to boil the milk for a half hour or longer and I believe the milk is then desensitized as well as we can make it.

Many of the cereals on the market are not good because they contain a mixture of alfalfa. Plain barley cereal or rice cereal are preferable. You can often see these rashes clear up within a few days.

Chairman Osborne: Is it true that eggs, wheat and milk constitute in your practice the principal allergenic substance when food is found to be at fault?

Dr. Ross: Yes and pretty well in that order.

Chairman Osborne: Do you ever prescribe an elimination diet in which eggs, wheat and milk are all eliminated at one time or do you prefer doing one at a time?

Dr. Ross: In the older infant where all 3 foods are being given, they may all have to be avoided at the one time if the eczema is severe and particularly if some clues have been obtained on skin tests. I am speaking of an infant over 6 months of age; in such infants elimination diets avoiding all 3 of these foods are started.

Chairman Osborne: I have had a number of pediatricians tell me that one of the things they do with these children is to put them on a soy bean milk for a period of 10 days, not allowing anything else. Do you think that would be a good procedure?

Dr. Ross: That is certainly a very restricted diet but for a short period of time it might be necessary as a trial period. You mention 10 days and I don't think that is long enough to give that diet proper trial. I believe it ought to be supplemented with an animal protein to get the best growth and development in these infants. I am in the habit of adding a small amount of meat protein to the soy bean diet.

Chairman Osborne: Dr. Ross and I have a difference of opinion to a minor degree; it is one of percentages and it is possible that it is due to many factors. One is that he sees a great many cases in children—he is a pediatrician. I see patients in consultation. Many of the patients he sees would have cleared up before I would get to see them. Our view is this: the food factor in this age group, we believe, is not as high as 50%. Many of us believe that it is 20 or 25% maximum in this age group rather than the 50% of Dr. Ross.

You must follow a definite scheme and plan in these food allergies. I would urge all of you as pediatricians to set down a definite plan of operation as Dr. Ross has outlined and follow that through so you are sure that there is no food factor in the eczema. If you do that and if the dermatologist would do that in cooperation with the pediatrician, we wouldn't have these large fields for disagreement.

Dr. Walter C. McKee, Chicago: May I state what I believe to be the discrepancy in the percentage. I think the average pediatrician has eliminated most of the food before you see them. That is why you have a smaller percentage.

Chairman Osborne: I would like to have Dr. Ross evaluate skin tests in the form of scratch and intradermal tests in this particular age group—just how much he uses them and of what value they are.

Dr. Ross: I think the skin testing in the past has probably been overrated. More conclusions were drawn from positive food tests which readily appear. We find we get positive tests from egg before the child has ever had an egg. It must be by trial feeding (feed and then withholding that food) that the proof is shown. I like to do the food test reaction and sometimes proof may be obtained.

Chairman Osborne: Since I believe that foods do not play as important a role as many other people believe they do, one must have something else to fill the vacuum. I am absolutely convinced that we are not paying enough attention to wool as an allergenic substance in these children up to the age of one year. Furthermore, I am convinced that dermatologists, pediatricians and allergists are not doing a good job of eliminating wool as a source of allergen.

Many men do not eliminate wool even in the presence of a positive skin test to wool. In our

experience it is necessary to eliminate all wool rugs, carpets and all woolen blankets from the house, not just from the room. Also, you must eliminate contact with woolen sweaters, clothes on parents and all those in contact with the child.

For about 12 years we have been doing microscopic examinations of dust for wool content. I am convinced that as the child gets older, foods in general become less important but that inhalants become more and more important. They spontaneously lose their food sensitization and they acquire other sensitizations. So as the child gets older it is more a problem of an inhalant allergy. Now, wool has been entirely overlooked in many ways. Never has anyone made sufficient effort to eliminate wool as an allergen. No one has ever done microscopic examination of house dust for wool fibers. Now it can be done until you get the percentage of wool in house dust down under about 3%.

Dr. Ross: The tendency to outgrow food sensitivity occurs between 3 and 5 years of age as a rule. They tend to develop strong sensitivity to any of these inhalant group of substances. I haven't been able to show in our testing that we get as high a proportion of wool sensitivity as Dr. Osborne gets with his testing; however, I think it is also very common in children over one year of age. They begin to develop more inhalant allergy and wool is one of the most important. I think other things must be considered. The child may sleep on a mattress that contains a great deal of kapok—we get a number of these cases. There are felt mattresses that even have cattle hair in them. We find that it is a multiple sensitivity—wool is an important part of these multiple sensitivities or there may be one or more that play an equal part. If you eliminate one you must also avoid another. I think this brings up the point of prevention. When we get a case that is sensitive in early infancy we invariably tell the parents you must avoid feather pillows. If the mattress is the ordinary felt type, it must be covered to avoid further sensitivity. When you know this child is in the allergic bracket it tends to develop inhalant allergy further on.

Chairman Osborne: As you can see, the members of this round table feel that in regard to eczema the first effort, no matter how old the child, whether the infant is under 6 months or the child 16 years of age, the first effort should be made to make an etiologic study. We are all agreed that it is the proper approach to eczema.

I would like to have Dr. Ross give an opinion as to the psychogenic factor in eczema.

Dr. Ross: I must say I have discounted the psychogenic factor entirely. Maybe I am very delinquent in this since some recent articles stress this rather strongly. I don't believe that the psychogenic factor comes into play—certainly not until the child is well over 10 years of age.

Chairman Osborne: We certainly should not overlook the psychogenic element in the older children and young adult or any adult as a matter of fact but it is more of a trigger mechanism and in my opinion never acts as a primary cause of atopic dermatitis. I think that too much emphasis has been placed on this in medical literature and in the press and that it is a good cover-up for ignorance in many cases. A ready answer to explain many things! I have never seen a psychiatrist who has cured a case of eczema. They just don't cure these cases. But the psychogenic element when it does exist, and it has been proved by experimental work, can have a marked effect upon the blood vessels in the skin and be a trigger mechanism affecting the severity or degree of any eczematous process. But it should never be regarded as a primary cause of such a process.

Dr. Albert J. Sheldon, Santa Ana, Calif.: What about washing diapers in detergents?

Chairman Osborne: It has been shown microscopically both by physicians and by the Laundrymen's Association that the use of any soap produces a gradually increasing deposit of insoluble salt of calcium and magnesium combined with the fatty acids of soap which pile up gradually layer after layer on the cotton fibres of diapers. When the material comes in contact with the acid secretion of the skin some of it is dissolved out and acts as an irritant. Now the best way to wash out the diapers in a simple detergent which is completely rinsable—Swirl, Dreft and Vel are the best. They are completely rinsable and they leave no deposit.

SPECIAL ARTICLE

AMERICAN BOARD OF PEDIATRICS

The written examination of January 11, 1952 was taken by 462 candidates, a larger number of candidates than on any previous occasion. A sample of the total number was selected for statistical analysis, the sample being made up of the grades earned by 284 candidates who by July 1, 1952 had stood the oral examination and could therefore be classified as having passed or failed the over-all examination. Two additional candidates who appeared for oral examination were given a "condition" in "Growth and Development"; the grades earned by these candidates are not included in the analysis. Of the total of 286 candidates the final results show: passed, 238; failed, 46; conditioned, 2.

The examination was divided into five sections, designated as A, B, C, D and E. Section A was composed of 100 false and true statements. All of these questions had been asked in previous Board examinations and all had been answered correctly by from two-thirds to three-fourths of the candidates. They were so selected to conform with the opinion of the Committee that the purpose of its examination is to discover the poorly qualified candidates and not to assign rank-order preference to the best qualified candidates.

Section B was designed to test the candidate's knowledge of infant feeding. Twenty questions, answerable by "yes" or "no," were presented in connection with three feeding formulas to be assessed by the candidate. The questions of both sections, A and B, offered the candidate only two choices (false or true; yes or no); a correct answer to any question was therefore assigned one-half of a grading point and a perfect score on Sections A and B would have been 60.

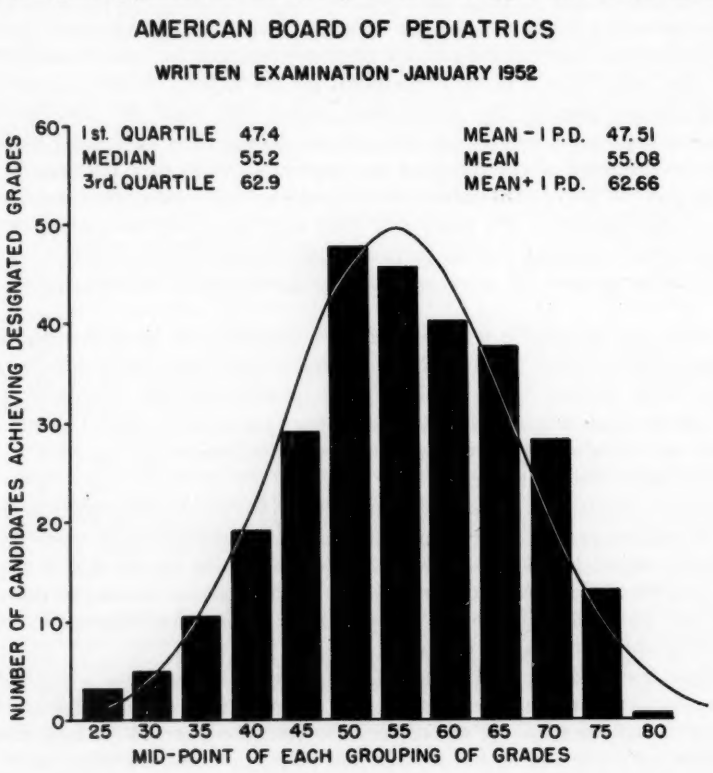
Section C consisted of 40 incomplete statements followed by five suggested completions. In common parlance such items are spoken of as "multiple-choice questions." For a candidate completely lacking knowledge the chances are that one out of each five questions could be answered correctly by guessing. In grading the examination this chance was ignored and each correct answer was assigned 1 grading point. Sections A, B and C therefore furnished 100 grading points.

Section D was made up of 20 sentences each consisting of two parts: a statement and a reason for the statement. The candidate was presented with a choice of five different responses to each question. He was requested to enter the letter "A" if both statement and reason were true and related as cause and effect; to choose the letter "B" if both statement and reason were true but not related as cause and effect; to write the letter "C" if the statement was true but the reason false; to select the letter "D" if the statement was false but the reason an accepted fact or principle; to inscribe the letter "E" if both statement and reason were false. Since an answer to each question demanded two correct responses from each candidate, a value of 2 grading points was assigned to each correct answer. The Committee believe that questions of this type demand more of the candidate than simple possession of factual knowledge, that in addition correct responses require clear thinking regarding cause and effect relationships.

Section E was made up of 10 questions, each consisting of five numbered words or phrases in a left hand column and three lettered words or phrases in a right hand column. As in Section D each question called for two responses from the candidate and

each correct response was assigned 2 grading points. Four of the items in the numbered left hand column suggested a feature common to one of the three lettered items in the right hand column. One of the items in the left hand column did not belong in the same category. The candidate's answer embraced a number and a letter: the number identified the item which did not belong and the letter the item characterizing the other four numbered items. The Committee believe that correct responses to this type of question also demand clear thinking.

The total grading points from the 190 questions of all types were 160. A candidate's



grade was obtained by dividing his score in grading points by 1.6.

The distribution of the grades earned by 284 candidates is presented in the diagram. The lowest grade was 23.1 and the highest was 77.5. Mean and median grades were both approximately 55. First inspection of the distribution columns of the diagram suggested that the examination was at last attaining a desired objective, namely, increased sensitivity for selecting the low grade candidates and decreased sensitivity for ranking the highly qualified candidates. Such a distribution would imply deviation from the normal curve of random scattering. Visual assessment of the degree to which deviation from the normal distribution was achieved is aided by the superimposition in the diagram of a normal curve of distribution computed from the mean and standard deviation of all

grades. A chi-square test of the significance of the deviations in the frequency of grades between those observed and those calculated on the assumption of a normal distribution does not reveal a statistically significant difference. The odds are 3 in 20 that a deviation as great or greater could have resulted from chance alone. Stated the other way the odds are 17 in 20 that the examination is beginning to realize its objective in range sensitivity.

As in previous years the reliability of the examination has been assessed by comparing the grade made by each candidate on his odd numbered questions with that recorded from his even numbered questions. The comparison reveals a "probable error of estimate" ($P.E._m$) of 2.78. The figure must be compared with that of 3.33 for the 1951 examination and of 3.39 for the 1950 examination. The increase in reliability is ascribed largely to the greater number of grading points on the 1952 examination. The examinations of 1950 and 1951 each furnished 100 grading points; this examination of 1952 yielded 160 grading points; the forthcoming examination of 1953 will have 250 grading points.

The reliability of the examination in predicting whether or not a candidate would pass the deciding oral examination is presented in table 1.

TABLE 1

Grade on Written Examination	Decision after Oral Examination		
	Passed (no.)	Failed (no.)	Passed (%)
Lowest quartile	36	31	54
Second quartile	61	13	82
Third quartile	60	4	94
Highest quartile	78	1	99
Totals	235	49	83

The Examinations Committee believe that the foregoing statistics indicate progress in the production of an improved written examination. Efforts to continue the progress are constantly being made. Currently, the analytic study of an examination includes the computation of an "index" of the actual value of each question asked. The index consists of the percentage of candidates passing the oral examination who knew the correct answer minus the percentage of candidates failing the oral examination who also knew the correct answer. It is already apparent that certain questions of all grades of difficulty are not effective in distinguishing between candidates who pass the oral examination and those who do not. Such questions will be eliminated in the future.

The American Board of Pediatrics as a whole has now decided that a candidate must earn a passing grade on its written examination before being permitted to appear for oral examination.

THE EXAMINATIONS COMMITTEE

Pediatrics

VOLUME 10 DECEMBER 1952 NUMBER 6

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

Your editor has asked a few physicians who have experience in the clinical, public health and educational aspects of some of the newer programs for handicapped children to prepare communications for this column. The first of these, Hearing Impairment in Childhood, is presented in this issue. The opportunities for helping children with impaired hearing which have been made possible by improvements in the vacuum tube, by specific therapy for middle ear infections, and by advances in speech training are among the most exciting in this decade.

A discussion of similar programs for children with epilepsy and with cerebral palsy are scheduled in future months.

HEARING IMPAIRMENT IN CHILDHOOD

By ARTHUR J. LESSER, M.D.*
Washington, D.C.

Prominent among the advances of the past decade is the progress made in the diagnosis, prevention and treatment of hearing impairment in childhood. These advances in audiology were made possible chiefly by the success of antibiotics and chemotherapy in the treatment of upper respiratory infections, and by the perfection of the tiny vacuum tube used in hearing aids. These developments, together with the recent increasing emphasis on services for preschool hard-of-hearing children have brought about considerable modifications of older concepts regarding hearing impairment. Hearing loss in childhood

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is frequently not static but susceptible to change for better or for worse. Today we have the skills and knowledge to prevent or minimize the development and progression of hearing loss among many children. The preventive aspects of conductive hearing loss are therefore less increasingly stressed—it is here that the medical profession makes a major contribution in this field. The pediatrician is directly involved, not only by his treatment of acute infection which so commonly used to result in permanently impaired hearing, but also by his knowledge of the growth and development of normal and handicapped children. His consideration of the child as a whole and as a growing individual takes on great importance in planning for the care and education of the child who has a handicapping hearing loss.

Terminology is somewhat troublesome, since there is varying use of the words deaf and hard-of-hearing. Some people also speak of the deafened to apply to those who lose their hearing after language has been acquired. Deaf to some means total absence of measurable hearing (which is rare), and to others, insufficient hearing for education in regular schools. The terms are relative and have meaning only insofar as the amount of hearing a person has can be measured. A child who fails to respond to one of the older methods of testing hearing and is therefore considered deaf, may be found to have considerable usable hearing when tested by the audiometer. The word deaf was established before there were any audiometers, which is to say, before there was any reasonably accurate method of measuring hearing loss. Since it has become possible to measure degrees of hearing loss, it has become apparent that many children once regarded as deaf do have some residual hearing. Frequently such children, if provided with hearing aids, taught speech reading, and given auditory and speech training, are able to hear adequately and, therefore, are regarded as hard-of-hearing rather than deaf. Deafness is today a label rather than a term with diagnostic meaning.

For these reasons hearing loss is classified in some clinics as follows:

mild to moderate (a threshold of 30-40 decibels by speech audiometry)
moderate to severe (a threshold of 40-70 decibels by speech audiometry)
profound (more than 70 decibels by speech audiometry)

The term applied to the diagnosis and treatment of communicative disorders caused by hearing loss is "clinical audiology."

It appears that about 5% of our school children have a loss of hearing of 9 or more decibels. About 1% of the child population is estimated to have a sufficient degree of hearing as to be considered handicapped.

The types of hearing impairment occurring among children are usually classified as follows:

a. Conductive hearing impairment

This is most commonly caused by acute or chronic infections of the middle ear. It also results from otosclerosis, congenital malformations, and temporarily from wax impactions. Conductive hearing impairment (except when due to otosclerosis) is largely preventable since we have effective means of treating middle ear infections.

b. Perceptive hearing impairment

The results from degeneration of the sensory cells of the internal ear. It is usually the high tones that are affected. It may result from infections affecting the auditory nerves, such as measles, mumps, meningitis, and from a familial degeneration of the cells of internal ear. Recently it has become recognized that this type of hearing impair-

ment may occur in infants as a result of maternal infections in the first trimester of pregnancy such as german measles.

c. Central hearing impairment

This is a nerve type hearing loss which has its origin in the central nervous system and may be due to tumors of the eighth nerve or to circulatory disorders of the cerebral blood vessels.

d. Psychogenic hearing impairment

This condition received extensive study among the armed forces during the war. It is unusual in childhood.

Case finding among children of school age is most effectively done through periodic audiometer tests. It is impractical in most schools to test annually. Testing the 2nd, 4th, 6th grades routinely is feasible and effective in most situations. Despite the long history of audiometer testing in this country, it was recently found that only 11% of children of school age receive audiometer tests. Routine periodic testing in schools is still the most effective method of case finding and should be employed on a wide scale.

The methods of audiometer testing in common use are:

1. Phonograph audiometer test

This is commonly used to test up to 40 school children simultaneously by playing a phonograph record and receiving the words (usually numbers) into sets of headphones. Retests are usually done with children who suggest a 9 to 15 decibel loss (the criterion varies). Children showing such a loss on the retest need to be studied individually. The phonograph audiometer is giving way to the pure tone screening test.

2. Sweep frequency test

This is an individual screening test, using a pure tone rather than words. The level of sound is placed arbitrarily at, for example, 15 decibels above the threshold of normal hearing and the tester "sweeps" through the frequencies. Children who miss at two or more frequencies should have diagnostic audiometry.

3. Massachusetts group pure tone test

This test employs the pure tone audiometer for group screening. Signals at four frequencies are delivered to groups of up to 40 children who indicate whether they hear the signal by underlining "yes" or "no" on the test sheet. Children who get more than two wrong answers receive an individual test.

In addition to periodic testing, children's hearing should be tested at any time a hearing loss is suspected by the teacher, nurse or physician. Indications may include apparent inattentiveness, speech defects, behavior problems and following contagious diseases or acute ear infections. Teacher observation alone cannot be considered a substitute for periodic audiometer testing. The watch tick and whispered voice tests have no place in a testing program.

The child who is found to have a hearing loss needs to have a careful pediatric and otologic appraisal and whatever medical and surgical procedures are indicated. Among many children with a conductive hearing loss medical or surgical treatment of acute or chronic pathology in the ears, nose and throat will frequently result in restoration to normal hearing or substantial improvement, with prevention of a handicapping degree of impairment.

There remains a sizeable number of children who are not helped by medical care or who are left with a significant hearing loss after treatment. It is not known how many

such children there are, but they probably constitute about 1% of all children. The plan for meeting the needs of such children must of course be developed individually, taking into account abilities in communication and the age of onset of the handicap in relation to the development of language. The modern audiology clinic with its multiprofessional staff, at its best developed in a teaching medical setting, is equipped to make the diagnosis and help the child develop and maintain a socially acceptable pattern of communication. This may include the use of a hearing aid, auditory training, lip reading and speech training. This involves more than a congregation of technical specialties; it involves an appraisal of the child's own individuality, his needs and capabilities and his reactions to his environment. Much depends on helping the parents to an understanding of the situation and enlisting their co-operation and participation in the treatment process. Considerable time may have to be spent in accomplishing this.

For school children whose audiograms show a loss in the neighborhood of 20-30 decibels, the most advantageous seating arrangement in school and instruction in lip reading will in most instances be found to be sufficient. Periodic medical and audiologic follow-up is of course necessary.

Children who have a hearing loss in excess of 30-35 decibels should be provided with carefully selected hearing aids. Most of these children will benefit considerably from the modern hearing aid if they are given adequate training in its use. They cannot be expected to use a hearing aid without such auditory training. Lip reading is essential and some may need speech training as well. Attendance in regular classes should be considered insofar as possible with provision for continuing special instruction as needed in lip reading, speech and auditory training. Some severely handicapped children will be found to do better in special classes in regular schools or in special schools.

Until a few years ago, most of the interest and work in hearing impairment centered about the child of school age, with little being done for the preschool child. In part this is due to the fact that there is a long history of work in education with hard-of-hearing children, while the contribution of the medical profession and electronics are much more recent.

However, it is a serious injustice to a young child with a handicapping hearing loss to wait until he is of school age to do something for him. Some audiology clinics are now making their most important contributions in the services they are providing preschool children. From every point of view, the time to begin to help the child is as soon as he is found to be in need of help—and the earlier the better. The development of language is normally dependent upon the ability to hear. Since the peak of language development is at 2 to 3 years of age, advantage should be taken of this period of maximum physiologic readiness, to help the preschool child with his speech. The too common alternative is to do nothing until the child is six years old and then send him to a residential school for the deaf. There are children in the residential schools for the deaf who could be living with their families, taking an active part in the hearing world with usual childhood associations, were adequate measures taken to provide the opportunities for them. There is an increasing awareness of these facts and more parents today are seeking help early for their young children. For those children, then, who have a hearing loss early in life, adequate attention to the development of communication in the preschool years becomes of crucial importance.

The diagnosis and measurement of hearing impairment in young children is not easy.

Infants and most preschool children do not provide the co-operation needed to carry out a pure tone audiometer test. When a child does not start to talk at the expected age, or when his speech is distorted and hardly intelligible it is not infrequent that an erroneous diagnosis of mental retardation is made. The technical difficulties obstructing the accurate testing of preschool children have now been largely overcome. By means of psychogalvanic skin resistance audiometry utilizing the conditioned response, the group at the Johns Hopkins Speech and Hearing Center have accurately measured the hearing of many infants and young children (as well as adults) without their co-operation or active participation.

The work with young children is going forward in an increasing number of speech and hearing centers in metropolitan areas throughout the country. Children 2 and 3 years of age in nursery classes are wearing hearing aids, learning to hear, learning to speak, reading lips, and learning how to live with their families and other children in the hearing world. They will, many of them, be better equipped to enter schools at the age of 6 years where they can continue to make progress if special education is available to them.

There is still considerable misunderstanding about the usefulness of hearing aids, some arising from the claims made for them by manufacturers and some from the emotional response of the patient or family to the wearing of an aid. A hearing aid of itself does not of course solve the problem of the person who has deficient hearing. It is an appliance, one of several measures that together may be used to improve one's communicative ability. It is an amplification system in miniature, and as such will amplify not only conversation, but the ambient noise as well. For adults who have gradually suffered a diminution of hearing and have become used to living with the loss of some sounds and the muffling of others, the return to the world of sound which we take for granted may be difficult and actually unwelcome. Many fewer hearing aids are worn than are sold, in part because of insufficient preparation in the use of the aid, and also because of the difficulty so many people have in accepting the realization of a permanently handicapping condition. A period of auditory training together with assistance as may be needed in helping the patient to an acceptance of the situation should be provided the person who is to wear a hearing aid.

Children usually respond more readily than adults to wearing hearing aids. For some it is the introduction to sounds they have never heard before. A passing fire engine, a bell ringing, the everyday sounds to which we are accustomed, may have to be identified and explained. Children benefit not only by auditory training in groups but they also need to continue to practice at home. People vary in the number of hours they wear an aid during the day and in their adjustment to its use. It is a good idea to wear an aid only for about 15 to 30 minutes a day initially. Listening at home to phonograph records, the radio, stories and simple conversation with the mother are all essential parts of the process of learning or becoming reacquainted with sounds. This accompanies auditory training in a speech and hearing center, where children may receive sound discrimination drills and increasingly complicated auditory experiences. To attain best progress in communication, children are introduced to lip reading during auditory training.

A great deal of the foregoing is predicated on the availability of specialized personnel and facilities in the community. The type of services and facilities we have been discuss-

ing are available in an increasing number of urban centers, are still very few however, and generally do not exist in smaller communities. One of the outstanding contributions of audiologists has been the concept that speech and hearing services can best be carried out in a medical setting and that a major part of these services are clinical in nature and not to be confused with education. The accomplishment of the objective of finding and helping the child who is hard-of-hearing, involving as it does the working together of several professions and organizations, requires a community program that is well planned to utilize existing resources and to relate itself to resources which may be outside the community, such as a teaching medical center. It is not possible today for every child who needs care to have access to these services, but we are seeing the development in several parts of the country of such community programs, through the efforts of the medical profession, the health and education departments and the voluntary agencies. State health departments, which for many years have engaged in audiometric screening as part of the school health programs, are adding diagnostic and treatment services for children with hearing impairment. Most of the problems can be handled by the physician in the community and serious complications prevented. For children requiring more complete audiologic study referral to a speech and hearing center is necessary but not practical today in many parts of the country. Not only the inadequacy of funds, but also of well trained audiologic personnel are major factors in holding back the development of speech and hearing centers. In addition to the state and federal funds used for services for children with hearing impairment in the State maternal and child health and crippled children's programs, the Children's Bureau has made grants at the university level for training in audiology. Increasing activity in State health departments and crippled children's agencies has greatly furthered the development of community programs in this field in the last few years.

The principal voluntary agencies are the American Hearing Society and the Volta Bureau from which literature for parents is available. The John Tracy Clinic in Los Angeles, California, has a home correspondence course to assist parents of preschool children.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

CURRENT STATUS OF VITAL STATISTICS

Reproduced below are the data and curves, by month, for 1951 and the first eight months of 1952, concerning estimated live births, marriage licenses, deaths and infant deaths. The material is reproduced from Vol. 1, No. 8, of the Monthly Vital Statistics Report of the National Office of Vital Statistics, Public Health Service, Federal Security Agency. The data are provisional and are based on reports received in registration offices. While subject to change when subsequent corrections are received, the figures reflect the true situation reasonably faithfully.

The 1952 birth rate, which appeared to be dropping below the 1951 figures, has increased again so that the cumulative rates are almost the same. This means, with the increase in total population, that the total number of births in 1952 will almost surely exceed the total number in 1951. Continued maintenance of such high birth rates will impose further burdens on children's health services and on public educational services later.

CHART 1

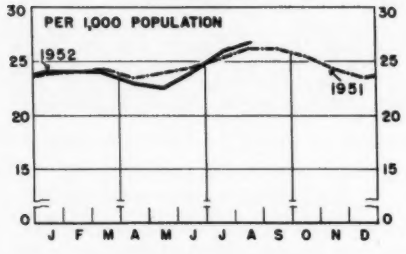
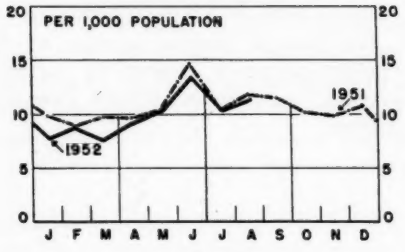


CHART 2



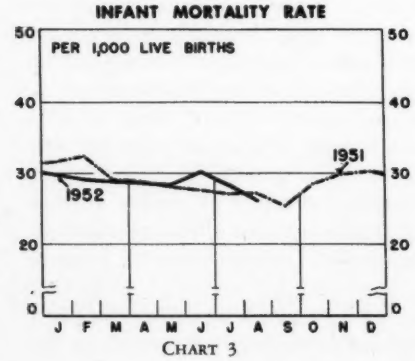


CHART 3

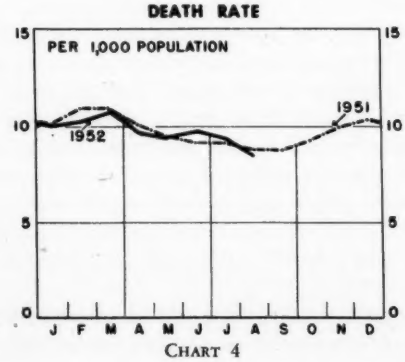


CHART 4

Marriage licenses continue to run below 1951 figures. The differences are not great, however, and the cumulative rate for the first eight months is only about 6% lower than last year.

Deaths in August were substantially lower than for July and the estimated rate for August, 8.5, is the lowest rate ever recorded in the U.S.A. for the month of August. The cumulative rate for the first eight months, however, is essentially the same as for 1951.

Infant mortality, perhaps the figure of greatest interest to pediatricians, continues at

VITAL STATISTICS: UNITED STATES, AUGUST 1951 AND 1952, AND CUMULATIVE FIGURES
Provisional

Item	August					January–August				
	No.		Rate			No.		Rate		
	1952	1951	1952	1951	Per Cent Change	1952	1951	1952	1951	Per Cent Change
Live births	352,000	340,000	26.7	26.1	+2.3	2,513,000	2,482,000	24.3	24.4	−0.4
Marriage licenses	150,232	152,366	11.4	11.7	−2.6	1,022,494	1,080,224	9.9	10.6	−6.6
Deaths	113,000	115,000	8.5	8.8	−3.4	1,002,000	995,000	9.7	9.8	−1.0
Infants deaths	8,900	9,000	26.1	27.2	−4.0	71,800	71,200	28.5	28.9	−1.4

its generally remarkably low level. In recent years August and September have been the months of the year with lowest rates (a far cry from the situation 40 years ago!) and August 1952 had the lowest August rate on record. For the first 8 months the infant mortality rate is slightly lower than last year and there is a possibility that 1952 may be another record low year. In absolute numbers one must not forget that had the rates of 40 years ago still been in existence, over these eight months more than 200,000 babies who have now passed their first birthday would have been dead before that time.

Continued low death rates and improving health indices are a mark of health progress. Persistent public health effort is needed to maintain this progress.

SPECIAL REVIEWS

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THE PRESENT STATUS OF GAMMA GLOBULIN

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The principles underlying the phenomenon of acquired immunity have found wide use for many years in the treatment and prophylaxis of infectious diseases, both by administration of preformed immune bodies such as antitoxins or specific antisera (passive immunity), and by the injection of toxoids, toxins and bacterial antigens (active immunity), as has been practiced for many years in pertussis and diphtheria. In the past few years studies relating to the isolation and clinical value of gamma globulin have opened new fields of usefulness in immune body therapy, especially as it concerns viral infections. It is the purpose of this paper to review the work that has led to current concepts about gamma globulin, and to indicate those areas in which it is believed to be of use.

Although the gamma globulin component of the plasma proteins has been defined previously, its present status reflects chiefly two developments of recent years. The first of these was the series of studies leading to practical technics for the fractionation of the plasma proteins and the isolation of many of them in relatively pure states. These studies have been carried out in this country chiefly by Cohn and his co-workers.[1–5] In brief, these procedures involve the simultaneous control of the various conditions concerned with the solubility of these proteins, namely, the concentrations of salts, proteins and a water-miscible organic precipitant (ethanol), and pH and temperature, and the adjustment of these to optimal conditions for the separation of components from the mixture. It has been shown that these manipulations not only separate the various plasma components, but also concentrate them. In the case of gamma globulin, the activity of the preparations obtained is approximately 25 times that of normal plasma.[2,6]

The second recent development of importance in relation to gamma globulin was the national blood-collecting program inaugurated by the American Red Cross during World War II,[7] which resulted in the pooling of plasma from adult donors in large amounts. The size of these pools is such that thousands of donors may be represented in a single lot of gamma globulin,[8] and this has tended to make fairly uniform the titers of antibodies against organisms and viruses indigenous to the geographic area in which the donors live.[9] Indeed, Enders,[6] by immunologic assay, has demonstrated this uniformity of potency in 62 different fractionation preparations collected in various parts of the country. In addition, he found an increase in influenza A antibodies following an epidemic.

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Thus, as Stokes[9] has pointed out, the uniformity of antibody levels in these materials may be conceived of as depending primarily upon the presence of endemic or recent epidemic diseases in the area in which the blood is drawn; the number and duration of antibodies resulting from particular infections; and the number of donors contributing to the pool. Since many infectious agents are widespread in their distribution, it may be reasonably expected that a large proportion of the population will have developed some degree of immunity to them by the time early adult life is reached. Further, it would seem reasonable to assume that such immunity could develop as the result of either frank clinical illness or inapparent (subclinical) infections. In most cases experience with such micro-organisms would be reflected by the continuing presence of neutralizing antibodies in the extracellular fluids. These concepts appear to furnish at least a partial explanation for the uniformity of antibody levels mentioned above and for certain clinical and epidemiologic observations, to be noted later.

By present technics, it has been estimated[10] that about 60% of antibody activity is recovered in Cohn's Fraction II, which consists of 95 to 98% gamma globulin. It has not been demonstrated that all the plasma antibodies occur in the gamma globulin fraction, but it appears that many antibodies against foreign protein antigens do occur here. (Some antibodies against polysaccharide antigens have been found in Fraction III-1.) Antibody titers in Fraction II are not significantly reduced by storage for nine months at room temperature or icebox temperature or by heating to 50° C. for as long as 14 days.[6] Its potency is not reduced when it is prepared from outdated blood (blood which has been held for more than 21 days at refrigerator temperature).[11,12]

We may now consider a variety of diseases in which gamma globulin has been used clinically and epidemiologically as a source of concentrated antibodies.

Measles

Evaluation of a series of clinical studies has brought both Stokes[9,13] and Janeway[10] to the conclusion that gamma globulin is the most satisfactory substance available at present for the prevention and attenuation of measles. Ordman, Jennings and Janeway[14] studied a group of presumed susceptibles with exposure within the family; of those receiving gamma globulin, 71% were protected against measles, 27% had modified measles, and there were 2% failures among 62 inoculated children. Of 46 uninoculated controls, only 7% failed to contract measles, 4% contracted mild measles and 89% developed measles of average severity. These authors felt that for children an intramuscular dose of 0.1 cc. per pound of body weight within 5 days after exposure was adequate in most cases for complete protection, and that if attenuation of the disease was desired, about ¼ of this dose should be used within 5 days after exposure. When the material is given later than this, somewhat larger doses should be used. The duration of protection is not known, but according to Ordman and his co-workers it is probably at least 2 weeks, but not as long as 7 to 10 weeks.

Stokes, Maris and Gellis[15] also noted striking attenuation or protection in a similar group with intrafamilial exposure. The dosage schedule recommended by these authors was as follows:

	Attenuation	Protection
5 years old or less	0.25-0.50 cc.	2.0-2.5 cc.
6 to 12 years old	1.0 -1.5 cc.	4.0-5.0 cc.

Or, for all ages up to 12 years, the dose per pound of body weight may be computed on the following basis:

Attenuation	0.02 cc./lb.
Protection	0.08 cc./lb.

These authors also treated early measles with gamma globulin in large doses (5 to 35 cc.). Of 31 patients injected when Koplik's spots were present, but no rash, there appeared to be modification of the disease in 13. Thus, there is suggestive evidence that large doses given early in the prodromal stage of the disease may modify its course.

Janeway[10] has noted that in patients in whom modified measles develops as the result of gamma globulin injection, postmeasles complications are about 1/10 as frequent as in unprotected groups of patients. He has also found gamma globulin to be effective in the control of measles in pediatric wards, and he feels that a satisfactory course in such circumstances is to isolate only the primary case, giving a protective dose of gamma globulin to exposed susceptibles and to susceptible new admissions for about three weeks thereafter. Janeway has also pointed out[16] the effectiveness of gamma globulin in measles prophylaxis in adolescents and adults. Banton and Mulford[12] felt that, in view of its scarcity, gamma globulin should be used for measles prophylaxis chiefly in children under 5 years of age and in debilitated or ill older persons. They felt that healthy older children could, in general, be permitted to have unmodified measles, "since permanent immunity may not invariably follow modified measles." The studies of Karelitz,[17] however, suggest that immunity following modified measles is lasting in the majority of individuals.

On statistical analysis, gamma globulin has been shown[16] to be more effective per unit volume than either convalescent serum or placental extract in measles prophylaxis.

Mumps

Clinical and epidemiologic work is not yet adequate for a thorough evaluation of the place of gamma globulin in mumps prophylaxis and treatment. The evidence available seems to indicate that in the case of mumps, antibodies must be administered in large amounts in order for any effect to be noted. Gamma globulin prepared from plasma pools obtained from the general population does not appear to protect exposed susceptibles when given in doses up to 50 cc.[9] Further, Gellis, McGuinness and Peters[18] found, in a mumps epidemic in an Army camp, that gamma globulin from normal plasma pools in doses of 50 cc. failed to reduce significantly the incidence of orchitis when given within 24 hours of the onset of parotitis. Gamma globulin prepared from mumps convalescent serum, on the other hand, when given in doses of only 20 cc. to a comparable group reduced the incidence of orchitis from 27.4% in the uninjected controls to 7.8% in the treated patients. This result was highly significant statistically. They also found that the titer of mumps complement-fixing antibody in the gamma globulin prepared from convalescent sera was about 10 times that of normal gamma globulin, 20 times that of pooled mumps convalescent serum, and 250 times that of normal pooled plasma.

Thus, the value of gamma globulin in mumps is limited by the amount of convalescent mumps serum available for fractionation; until gamma globulin prepared from such serum is available in large amounts, it probably should be used only for the treatment of adult males in the first 24 hours of the disease, the object of treatment being to prevent or to attenuate orchitis.[13] Treatment of adult females is not at present as justifiable,

since the lack of a tight, confining tunica albuginea around the ovary prevents oophoritis from being as serious a complication of mumps as orchitis.

Infectious Hepatitis

The first use of gamma globulin for prophylaxis against infectious (epidemic) hepatitis was recorded by Stokes and Neefe,[19] who used it in an outbreak at a summer camp in Pennsylvania. The use of the material was suggested by several considerations. First, no jaundice had been reported following thousands of gamma globulin injections for measles prophylaxis, suggesting that the virus was either destroyed or inactivated during preparation of the globulin or was not isolated with this fraction, or that neutralizing antibodies were present in the material. Second, it was known that the hepatitis virus is present in the blood during the pre-icteric and early icteric phases of the disease, which would allow for contact between virus and gamma globulin. Third, it was felt that the long incubation period of infectious hepatitis would facilitate the use of gamma globulin. The material was administered intramuscularly in doses of approximately 0.15 cc. per pound of body weight. Over the ensuing months there was a striking reduction in the incidence of hepatitis in the injected group as compared with a control group of similar composition. Also, the data suggested that individuals receiving the globulin earlier in the incubation period were more completely protected, and that persons who developed hepatitis despite gamma globulin administration had attenuated disease.

The efficacy of this material in protecting against infectious hepatitis under field conditions was demonstrated by Gellis and his coworkers[20] in two outbreaks in Army units during World War II using about 0.06 cc. per pound. These authors felt that the material conferred "a period of passive immunity of at least 6 to 8 weeks." Further studies on the nature and duration of this protection will be discussed below.[21]

Havens and Paul[22] studied an institutional outbreak primarily involving children. Doses varying from 0.06 to 0.12 cc. per pound of body weight were shown to be effective in protecting against infectious hepatitis. They found no evidence either for or against attenuation of the disease by gamma globulin. In all outbreaks thus far studied it has appeared that gamma globulin does not protect within the first 5 to 6 days after injection; that is, when the material is given this late in the incubation period the course of the disease is unaffected.

In a study on treatment of early, pre-icteric hepatitis with gamma globulin in large doses, Gellis and his co-workers[23] noted no beneficial effects. Studying a treated group and a control group, they found no significant difference in the incidence, severity or duration of jaundice; in the duration of positive laboratory studies; or in the frequency of relapses. Thus, from the evidence at present available, it would appear that gamma globulin, in the doses and under the circumstances thus far explored, is not efficacious in infectious hepatitis either in the late stages of the incubation period (within 5 to 6 days of the onset of symptoms) or once symptoms have appeared.

In a recent report, Stokes, Farquhar and Drake and their associates[21] recorded evidence that recent batches of gamma globulin are as effective in prophylaxis against infectious hepatitis as are older ones. They also found, in an institutional outbreak, that doses as small as 0.01 cc. per pound body weight were protective. The implications of this finding, in view of the limited availability of gamma globulin, are great. These workers also found, in studying institutional epidemics, that a single injection of gamma globulin afforded protection against the disease for periods of at least 5, 8 and 9 months in three such

outbreaks, despite continued heavy exposure. The implications of this finding are discussed below.

In view of the fact that the incidence of infectious hepatitis falls off rapidly after the age of 30 years, and considering also that gamma globulin prepared from normal adult plasma pools has proved to be effective in preventing infectious hepatitis in exposed susceptibles, and therefore presumably contains a high titer of protective antibodies, it has been suggested[9, 13] that a large proportion of the population has been immunized against the disease by the time early adult life is reached, either by frank clinical hepatitis or by inapparent infection. That such may not be the case in serum hepatitis is suggested by the fact that no similar fall-off in incidence has been noted after early adult life is reached, and by the clinical experience with gamma globulin, which we may now consider.

Serum Hepatitis

The results of studies on gamma globulin in serum hepatitis have not been as clear-cut as in the case of infectious (epidemic) hepatitis. A study in an Army hospital by Grossman, Stewart and Stokes,[24] in which 10 cc. of gamma globulin was given to alternate battle casualties and was repeated in the injected group after one month, suggested that the material would be of value in protecting against serum hepatitis. Omitting cases occurring within one week after the injections were given, the injected group had an over-all incidence of hepatitis of 1.3%, while the uninoculated control group had an incidence of 8.9%. It was also found that the cases occurring in the injected group were in general mild ones, which led the authors to believe that some degree of attenuation had been achieved through the use of gamma globulin.

In another study[25] in an Army hospital, differing from the above only in that a single dose of 10 cc. of gamma globulin was used, there was no significant difference in the incidence of hepatitis in the injected and control groups, and there was no difference in the relative lack of effect of sera collected from the Eastern United States or from the Far West and Northwest. The authors felt, however, that gamma globulin in the dose used retarded the onset of serum hepatitis by an average period of 18 days, and this prolongation of the incubation period was statistically significant.

Preliminary studies in human volunteers[26] appear to support the idea that gamma globulin is not as efficacious in protecting against serum hepatitis as against infectious (epidemic) hepatitis.

In general it would seem that studies thus far are conflicting in regard to serum hepatitis, and that present knowledge does not allow a final evaluation of the place of gamma globulin in the handling of this disease. It appears doubtful from the epidemiologic studies mentioned above and from the early studies in human volunteers that a large proportion of the general population has neutralizing antibodies against serum hepatitis in the circulation, or that the gamma globulin in current use contains titers of protective antibodies against serum hepatitis as high as those which it apparently contains against infectious (epidemic) hepatitis.

German Measles

Studies on the adequacy of gamma globulin in protecting against german measles are not at present extensive enough to allow final evaluation; there is some evidence, however, that a definite protective effect is exerted. Stokes[13] has recorded an instance in

which a nurse with rubella intimately exposed five presumably susceptible roommates. Each of the latter received 5 cc. of gamma globulin four days after exposure; no secondary cases developed. He also reported the exposure of a ward of 13 infants and children, all presumably susceptible, to an infant with rubella. There were no secondary cases following the administration of 2 cc. of gamma globulin four days after exposure.

The Committee on Public Health of the New York County Medical Society has reported studies in an institutional outbreak of rubella.[27] In this epidemic 320 children were intimately exposed; 151 received gamma globulin in an average dose of 0.1 cc. per pound of body weight; 169 children served as uninoculated controls. Although 58 children were later eliminated from the study for a variety of reasons, the results appeared to be clearcut; two cases occurred in each group within three days after injection. Omitting these cases, the following results were obtained:

Up to the 10th day	No cases in either group
From the 10th to 18th days	13 cases among the controls No cases in the treated group
On the 19th day	3 cases among the controls 4 cases in the treated group
From the 19th to 35 days	9 cases in the controls 6 cases in the treated group

No note was made as to the severity of the cases occurring in the treated group. It would appear that gamma globulin, in the dose used in this study, when given on the day of exposure, exerts some protective effect against rubella in children. The authors felt that this protection was lost some time before the 19th day after administration. The two cases occurring within three days after injection suggest that no protection was afforded when the material was given as late in the incubation period as three days prior to the onset of symptoms. McLorinan[28] has reported on the use of gamma globulin prepared from convalescent serum, and feels that it has been effective in prophylaxis in a dose of 4 cc.

The studies mentioned point to the need for additional controlled experience in this field, and this need is pointed up by the deleterious effects on the fetus that may follow the occurrence of rubella in pregnancy.[29]

Poliomyelitis

Controlled clinical and epidemiologic studies on prophylaxis against poliomyelitis with gamma globulin are lacking, but there is some evidence in studies on animals which points to the need for such a controlled trial. In addition some clinical studies have been done, which, while not conclusive, also are not inconsistent with the animal studies.

Gamma globulin has been shown to contain large amounts of neutralizing antibodies against the three known immunologic types of poliomyelitis virus, the Lansing, Brunhilde and Leon strains.[30] These have been found to be present in approximately equal titer. Furthermore, 0.1 cc. injected intraperitoneally will protect a mouse against simultaneous intracerebral inoculation of the Lansing strain of virus (Stokes and Henle[13]). These studies have been confirmed by Kramer,[31] using the Armstrong strain in mice. These preliminary results in animals suggest strongly that, despite the low incidence of

clinical poliomyelitis, a large proportion of the population has had contact with these viruses sufficient to result in significant antibody titers. In addition to these animal studies, some human studies have been done. Most of these have been attempts to protect chidren during epidemics by injection of whole blood from a parent. While the results of these studies have not been entirely clear-cut, there has been an increasing belief among those working in the field that such measures did afford some degree of protection.[32] Bloxsam,[33] in 1949, reported the use of gamma globulin in an epidemic of poliomyelitis in Texas. While this study was not adequately controlled, it may be of interest to note that of 35 siblings of poliomyelitis patients, only three developed poliomyelitis following injection of 2 cc. of gamma globulin, and these cases occurred on the first, second and third days, respectively, following its administration. Among 806 nonsiblings of poliomyelitis patients who received gamma globulin, there was but one subsequent case, and this occurred 42 days after injection of the globulin. It may be that gamma globulin was injected too late in the incubation period to be of any protective value in the first three cases, and that the fourth case occurred after antibody titers had fallen to ineffectual levels.

These and other studies have pointed to the need for a large-scale epidemiologic trial in poliomyelitis, and such studies have recently been reported by Hammon and his associates.[34-36] In a carefully controlled series of studies, 54,772 children between the ages of 1 and 11 years were inoculated, half with gamma globulin and half with gelatin. These children resided in epidemic areas at the time of the tests. In a preliminary report on the outcome of these studies, Hammon's group has demonstrated significant protection against paralytic poliomyelitis from the second through the fifth week after injection. In addition, children receiving gamma globulin who developed paralytic disease within the first week after injection appeared to have had some modification of the illness. Laboratory studies bearing on the effect of this material on inapparent infection and the development of active immunity are forthcoming.

The proper place of gamma globulin in prophylaxis against paralytic poliomyelitis, either alone or in combination with actively immunizing agents, is yet to be worked out, in terms of application of the above findings in the field. If it can be shown that gamma globulin does not interfere with the development of active immunity, these studies furnish a sound scientific foundation for further work on the establishment of a program of passive-active or active immunization against paralytic poliomyelitis.

That the drug has no place in the therapy of established poliomyelitis has been demonstrated by the study of Bahlke and Perkins,[37] who found it to have no effect when given to alternate preparalytic cases during an epidemic.

Other Diseases

Gamma globulin has been given in large doses to patients with scarlet fever,[38] and the results were said to compare favorably with those obtained with scarlet fever antitoxin. Both groups of patients were compared with a series of untreated controls but no comparison was made with a group given optimal antibiotic therapy. Epidemiologic studies in scarlet fever or streptococcal sore throat have not been reported.

Bower, Affeldt and West[39] gave gamma globulin to patients with the so-called anginose type of infectious mononucleosis, and reported results somewhat better than those obtained with penicillin; however, this was a small, inadequately controlled series, and it

is difficult to tell from the case reports given how much of the observed improvement might have reflected the natural course of the disease.

An interesting animal study was that of Cheever and Daikos,[40] in which virus neutralizing antibody for herpes simplex was found to be present in human gamma globulin, by means of protection tests in mice. Studies of the use of gamma globulin in human herpetic infections have not yet been reported.

Janeway[16] mentions that the material has received limited trial in protection against varicella, but with no protection observed. Dosage in these trials has ranged from 5 to 20 cc.

Use of Gamma Globulin Preparations

Current gamma globulin preparations should only be used intramuscularly. Intravenous use may result in serious reactions.[41] Janeway[16] has emphasized the safety of the material when it is given intramuscularly. The following figures are taken from Janeway's summary of 1843 injections, following which there were 32 reactions in 31 patients, or 1.7% reactions. It will be noted that half the reactions were local and half were general, chiefly fever, with one anaphylactoid type.*

	# Cases	*# Reactions*	*% of total Reactions*
Local soreness or swelling	16	16	50
Fever	11	12	38
Headache	1	1	3
Dizziness	1	1	3
Hyperactivity	1	1	3
*Chills, fever, orbital edema	1	1	3
	31	32	100

The danger of the transmission of the virus of serum hepatitis in gamma globulin preparations as currently used in the United States appears negligible.[42] Large numbers of patients have been carefully followed after these injections for the appearance of hepatitis between 50 and 200 days after injection, but no clear-cut case has been found. The conclusion appears justified that the methods of preparation of gamma globulin by Cohn's technic inactivate the virus, eliminate it from the gamma globulin fraction, or neutralize it. Since each lot of gamma globulin represents the pooled plasma of about 2000 donors, and since World War II plasma pools of only 50 to 70 donors resulted in an incidence of serum hepatitis of about 5%, many cases should have occurred after gamma globulin administration unless such elimination of the virus were taking place.

Mechanism of Action

The actual mode of protection by gamma globulin against a variety of viral diseases is not yet known, but certain observations have led to the formation of some theories.

As mentioned above, Gellis and his co-workers,[20] early in the studies on gamma globulin, felt that protection against infectious hepatitis was probably due to a passive immunity resulting from the injection of large quantities of antibodies contained in the gamma globulin. More recently, Stokes, Farquhar, Drake and their associates[21] have found that the material protects against infectious hepatitis for long periods of time, and indeed, as pointed out above, the duration of this protection was observed to be at least 5, 8 and

9 months in three institutional outbreaks studied. These authors have hypothecated that the mechanism of protection probably involves the superimposition of an active immunity upon the waning passive immunity provided by the injection of the gamma globulin; that is, in an epidemic situation, the continuing exposure of the injected individuals to the virus in the cases occurring around them produces active immunity to the disease without the occurrence of clinical illness, and this active immunity is produced simultaneously with the waning of the passive immunity which has resulted from the globulin injection. The possibilities of continuing passive immunity or of active immunity resulting from injection of gamma globulin have not yet been completely evaluated.

The soundness of this idea will best be evaluated after careful studies, not only in infectious (epidemic) hepatitis, but in the other diseases in which gamma globulin has been shown to be of use. It is possible that the technic of passive-active immunization, using gamma globulin as a source of concentrated antibodies, will eventually find practical clinical application in the protection of human newborn or older children against a variety of diseases.[21]

Summary and Conclusions

The studies which have led to the availability of gamma globulin for clinical use have been briefly reviewed, including those having to do with isolation, immunologic assay, purity, stability, safety and technic of administration.

Its use in a variety of virus infections has been described and reviewed, and the preliminary nature of many of these studies has been emphasized. It has been established that gamma globulin is an effective prophylactic agent not only in measles but in infectious (epidemic) hepatitis. Gamma globulin prepared from convalescent mumps serum is useful in reducing the incidence of complicating orchitis in mumps. There is evidence that it may be a valuable prophylactic agent against rubella. It gives promise of value as a prophylactic against poliomyelitis, although the definitive field trials are yet to be conducted. Its proper application in serum hepatitis and varicella is yet to be defined.

It would seem, in view of the uniformity of antibody titers, where it has been possible to measure these, and in view of the uniformity of protection from gamma globulin in a variety of conditions in which it has been tested, that the donors from whose plasma the material has been prepared have in general been immunized against these diseases, either by clinical or subclinical infection, and this reasoning may be extended to the general population from which these donors are drawn. Thus, aside from the practical clinical and epidemiologic applications which are appearing for gamma globulin, it shows promise of becoming an important tool in research in the basic biology of host-parasite relationships, including certain aspects of immunity as well as virus ecology.

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NEWS AND ANNOUNCEMENTS

Paul György, M.D., Professor of Nutrition in Pediatrics at the University of Pennsylvania and Pediatrician-in-Chief at the Hospital of the University of Pennsylvania, will deliver the twenty-first annual series of the Benjamin Knox Rachford Lectureships on Tuesday evening, Feb. 10, and Wednesday evening, Feb. 11, 1953, at 8:30 P.M. in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. The titles of his lectures are (1) "Human Milk versus Cow's Milk in Infant Nutrition" and (2) "Protein Nutrition and the Liver."

* * *

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The Board announces the following schedules for the coming examinations: Written examinations under local Monitors will be held on Friday, Jan. 16, 1953. This is the only written examination which will be given in 1953.

The oral examinations will be:

Baltimore—Feb. 20, 22 and 23, 1953.
Memphis—March 27, 28 and 29, 1953.
Philadelphia—May 1, 2 and 3, 1953.

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